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Dan A. Oren
*Yale University*


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Dan A. Oren

(Signature of author)

Dan A. Oren

(Printed name)

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# THE RISK FACTOR APPROACH TO NEPHROLITHIASIS:

## AN ANALYSIS OF THE FIRST 229 PATIENTS EXAMINED AT THE YALE-NEW HAVEN MEDICAL CENTER RENAL STONE CLINIC

by Dan A. Oren

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SUMMARY

Historical and laboratory data from the first two hundred twenty-nine patients who were evaluated in the Renal Stone Clinic at the Yale-New Haven Medical Center were analyzed according to type of renal calculus, in an attempt to examine various risk factors leading to the development of the specific type of stone. Three patients had cystine stones; six patients had uric acid stones; nine patients formed magnesium ammonium phosphate stones; seventeen formed calcium phosphate stones; and two hundred one formed calcium oxalate or mixed calcium stones. The major focus of this analysis was on the identification of preventable risk factors in patients with the garden-variety calcium oxalate stone. One or more risk factors were identified in the vast majority of these patients, and several novel aspects of certain risk factors were discovered.

INTRODUCTION

Renal stone disease is a medical condition of far more than academic interest. Occurring in approximately three per cent of the American population, renal stones account for one in every 1000 hospital admissions in the United States. (Broadus, 1981) The colic that renal calculi can cause is said to be "one of the more severe, frightening pains encountered in medical practice." (Walker, 1980) Because of the growing body of data implying that nephrolithiasis is often preventable, great effort has been expended in the characterization of the disease and the habits that may cause the disease. Although the growing body of knowledge is continually expanding, many of the treatment modalities for nephrolithiasis have not kept up with the growing knowledge base. For that reason this study was designed to examine the records of the first 229 patients at the Yale-New Haven Medical Center Renal Stone Clinic to complete a metabolic screening evaluation for underlying causes of nephrolithiasis.

Renal stone disease, in essence, is a constellation of several entities. In general the term "nephrolithiasis" refers to calculi primarily composed of cystine, magnesium ammonium phosphate, uric acid, calcium phosphate, calcium oxalate, or mixed calcium oxalate-calcium phosphate. (Mixed calcium oxalate-calcium phosphate stones refer to those calculi which are mostly composed of calcium oxalate, but have a calcium phosphate composition greater than twenty per cent.) As will be seen, the crystallographic stone type forms a rational basis by which to subdivide patients with renal stone disease, and the following schema will provide the organizational format for this thesis:

I. Cystine Stones
II. Uric Acid Stones
III. Magnesium Ammonium Phosphate Stones
IV. Calcium Phosphate Stones
V. Calcium Oxalate and Mixed Calcium Stones
    A. Calculi as a secondary manifestation of other illnesses

B. Calculi as a primary disease--"garden-variety" stones

Several points regarding this schema are noteworthy at this juncture. Although this thesis will concentrate mostly on calcium oxalate stones, it will review the other stone types and make a clear distinction between calcium phosphate and calcium oxalate stones, a distinction often not made in the existing literature on the subject. The category of calcium oxalate stones and mixed calcium stones will be considered in two parts. As secondary manifestations of other illnesses (only a small portion of the total are in this category), their underlying pathophysiology will be reviewed. For calcium oxalate and mixed calcium stones forming without a known primary illness, the risk factor concept will be introduced, highlighting the risk factors of family history, hypouresis, hypercalciuria, and hyperuricosuria. Although treatment and outcome are beyond the scope of this study, the risk factor approach to renal stone disease allows the hope that elimination of some or all of the statistical risk factors may, in fact, prevent or significantly lower the subsequent incidence of renal stone formation in this patient population.

Cystine Stones

Cystine is the least soluble of all of the naturally occurring amino acids. In normal urine its maximum solubility is approximately 300 mg/L. These stones are formed only by homozygous cystinurics whose genetic defect in renal tubular amino acid reabsorption causes them to excrete 600 to 1400 mg of cystine daily. With the urine being oversaturated with cystine, spontaneous formation of cystine crystals will take place, contributing to the formation of cystine stones. An alkaline urine can increase the solubility of cystine, but disorders of urine acidification alone are not responsible for cystine stone formation.

Because the intestinal transport system for cystine is either absent or defective in almost all patients with cystinuria, the cystine that is excreted in the urine must be derived endogenously from the hepatic metabolism of dietary methionine. Because the transport system is missing in the renal tubules, likewise, cystine reabsorption does not take place and cystinuria results.

Any patient with a history of recurrent renal calculi is a potential cystine stone former. A diagnosis may be suggested by an early age of onset of stone disease. Definitive diagnosis is made by stone analysis, demonstration of cystine crystalluria, or by quantitative urinary amino acid analysis.

This study will reinforce the statement that hypercystinuria is associated with formation of cystine stones and indicate its rarity within a renal stone clinic population.

Uric Acid Stones

Uric acid stones are usually pure, affect mostly middle-age males, and account for approximately five per cent of stone disease in Western countries. As the final breakdown product of purine metabolism in humans, uric acid production and excretion are affected by dietary purines as well as endogenous purine production. Because the rate of metabolism of endogenous purines in a given individual remains constant under normal circumstances, variation in uric acid production is largely a function of dietary purine intake. Uric acid is excreted into the urine through a complex system of proximal tubular reabsorption, tubular secretion, and post-secretory reabsorption. Tubular reabsorption is the dominant quantitative process governing the amount of uric acid excreted.

Whether the urine uric acid will precipitate to form a stone is largely a function of the ambient urinary pH. An acidified urine will tend to shift the equilibrium between uric acid and its urate salt in the direction of the acid form. Uric acid is far less soluble than its urate salt. Because the $pK_a$ of uric acid is 5.75--in the center of the physiological range for urine pH--the relative concentrations of uric acid and urate salts are exquisitely sensitive to urine pH. For example, given a urine uric acid excretion of 1000 mg per day at a pH of 6.0, the amount of free uric acid present would be 360 mg. But at a pH of 5.0, the amount of free uric acid present would be 950 mg. Since the ultimate solubility of uric acid in urine is about 100 mg/L at pH of 5.0, and 1500 mg/L at pH of 7.0, the shift in pH by one could be the difference between precipitation and solubility for uric acid.

Diagnosis is best made through laboratory analysis of a stone. Because uric acid stones are radiolucent, they can only be suspected from an intravenous pyelogram. This study will support the concepts that hyperuricosuria and hypouresis should be considered as physical chemical risk factors associated with uric acid stones.

Magnesium Ammonium Phosphate Stones

Magnesium ammonium phosphate stones (MAP) stones are a relatively rare but extremely morbid type of renal calculi. As with cystine and uric acid stones, MAP stone formation is a logical consequence of physical chemistry. MAP stones are composed of struvite ($MgNH_4PO_4*6H_2O$) admixed with small amounts of carbonate-apatite ($Ca_{10}(PO_4)_6CO_3$). In sterile urine, the solubility product of struvite is never exceeded, and MAP stones do not form. The pathological presence of urease-producing bacteria can cause an alkaline urine and increased concentrations of ammonium, car-

bonate, and relatively insoluble, multiply charged phosphate ions. These charges oversaturate the urine with respect to both magnesium ammonium phosphate and carbonate-apatite, quickly leading to struvite stone formation. Urease acts on urea in the following sequence:

$$\text{Urea } (CO(NH_2)_2) + H_2O \xrightarrow{\text{Urease}} 2\,NH_3 + CO_2$$

$$2\,NH_3 + 2\,H_2O \rightleftharpoons 2\,NH_4^+ + 2\,OH^-$$

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

$$H^+ + HCO_3^- + 2\,OH^- \rightleftharpoons CO_3^{-2} + 2\,H_2O$$

With some ninety per cent of clinical isolates of Proteus, Staphyloccus aureus, and Bacteroides species producing urease and some thirty per cent of Klebsiella and Pseudomonas acting in the same manner, all of these bacterial strains have been clinically implicated in series of MAP stone patients. Proteus species, however, have been the most common isolate.

The basic prerequisite for a MAP stone is an abnormality that predisposes to urinary tract infection. These derangements include megaureter, ureteral reflux or obstruction, ileal conduits, nephrostomy drainage, medullary sponge kidney, neurogenic bladder, or the presence of any non-MAP stone. Diagnosis is made thorugh radiologic visualization of a staghorn calculus or by crystallographic analysis of stone material. This study confirms previous reports that in a substantial proportion of MAP stone patients urine colony counts of urease-producing bacteria were less than 100,000 per milliliter. (Broadus, 1981). It reveals, however, a lower incidence of associated abnormalities associated with non-MAP stone formation than reported by others. (Smith, 1976)

Calcium Phosphate Stones

Unlike some conventional considerations of nephrolithiasis, this study emphasizes that calcium phosphate stones (a relatively rare phenomenon) sthould be considered as distinct from the common calcium oxalate stone. (Coe, 1973, Coe, 1974, Ullmann, 1982).

An essential feature of calcium phosphate stones is that they form in a sterile alkaline urine. The importance of the urine pH is rarely appreciated. With the concentration of $HPO_4^{-2}$ rising rapidly in the presence of increasing pH, the components of a calcium phosphate stone reach concentrations of supersaturation, and ultimately oversaturation, which forces calculus formation. (Broadus, 1981, Nordin, 1973). Since, as this study confirms, calcium phosphate stones only form in a sterile alkaline urine, their presence suggests an underlying mechanism associated with a persistently alkaline urine.

A normal kidney maintains the pH of the extracellular fulids by entirely reclaiming the filtered load of bicarbonate and by excreting a quantity of fixed acid equal to that produced endogenously. Almost all of the filtered bicarbonate is reabsorbed in the proximal tubule. The distal tubule operates to remove remaining bicarbonate and set the final urinary pH. The normal kidney can achieve a final urinary pH of 5.0 or lower. (Brenner, 1980)

One acidification disorder seen in calcium phosphate stone patients is complete distal renal tubular acidosis (RTA). Patients with this illness are rarely able to produce a urine with a pH of less than 5.5. RTA can be caused by genetic factors, Sjögren's syndrome, medullary sponge kidney, Ehlers-Danlos syndrome, amphotericin, obstructive uropathy, and several other miscellaneous conditions. (Kathpalia, 1980)

The resulting acidosis inhibits citrate production in the renal cortex, leading to a reduced citrate excretion rate. Because the citrate can then have less of an ef-

fect on binding urinary calcium into soluble complexes, RTA acts as a double-edged sword to cause calcium phosphate stone crystallization. RTA may also stimulate hypercalciuria by causing a defect in distal tubule calcium reabsoprtion or through mobilization of bone calcium, as bone minerals are used to buffer serum acids. Incomplete distal RTA, in which there is no systemic acidosis although the urine is alkaline, might also lead to calcium phosphate stone formation, but this question was not evaluated in detail in the present study. (Broadus, 1981)

Medications may also predispose a patient to form calcium phosphate calculi. (Parfitt, 1969) As a carbonic anhydrase inhibitor, acetazolamide will inhibit proximal tubular bicarbonate reabsorption, simultaneously inhibit citrate production, decrease the excretion of ammonium ion and titratable acid, and increase the urine alkalinity--in effect causing secondary or "exogenous" RTA. Chronic low-dose ingestion of calcium or sodium bicarbonate antacids may cause urine alkalinity and calcium phosphate stones as well. (Broadus, 1981)

Diagnosis can be made only through crystallographic analysis.

Calcium Oxalate and Mixed Calcium Stones

Stones containing calcium oxalate make up the lion's share of the stones. This category was defined as including patients who met at least one of the following criteria: 1) crystallographic analysis of a renal calculus which showed that the stone was composed of at least fifty per cent calcium oxalate, and/or 2) radiologic examination showing the presence of a radioopaque stone (or stones) in a patient with no suggestive evidence of another stone type. Of the 179 patients in this group, 156 (87%) satisfied the first definition. Predominantly males are afflicted with this stone

type. (Johnson, 1979) The risk factor concept may be applied most fruitfully to this population.

A short review of the physical chemistry associated with the formation of calcium oxalate-containing is in order. The underlying concept to be addressed is the equilibrium between the solid crystal and dissolved ionic phases of a solute such as calcium oxalate. In an "undersaturated" system, the addition of solid phase material to the system leads to the complete dissolution of the solid material. When sufficient solid phase material is added, however, the system becomes "saturated." In this condition, added solid phase material can only partially be dissolved into its ionic components. If one removes the solid from this system, one is left with a "saturated" solution of ions dissolved in water. When sufficient quantities of a concentrated solution of any of the solute components are added to the "saturated" solution, then the "saturated" solution will become "oversaturated," and solid crystals will spontaneously nucleate (i.e. precipitate) out. Although the case of calcium oxalate in urine is a far more complex system than that in water (involving numerous soluble components and ion-ion interactions) the aqueous system may be seen as a model for precipitation of calcium oxalate crystals in urine. When sufficient quantities of a concentrated solution of any of the solute components (e.g., a hypercalciuric urine in the distal renal collecting tubules is added to a "saturated" urine in the renal collecting ducts), oversaturation may occur and calcium oxalate stone formation may occur. Because calcium oxalate is less soluble in normal urine than either calcium phosphate, uric acid, magnesium ammonium phosphate, and cystine, it is more sensitive to abnormal urinary perturbations than any other stone type. This fact likely accounts for the great frequency of calcium oxalate stone disease observed among patients with nephrolithiasis (Broadus, 1981). This fact also underlies the

clinical utility of the risk factor concept in practice, some of these risk factors including abnormalities which have no direct influence on calcium or oxalate metabolism per se.

To facilitate consideration of this stone type, the following etiologic and epidemiologic schema will be followed:

I. Calcium Oxalate Stones Secondary to Established Primary Illnesses
   A. Primary Hyperparathyroidism
   B. Enteric Hyperoxaluria
   C. Renal Tubular Acidosis
   D. Sarcoidosis
   E. Others: Vitamin D Excess, Immobilization, Uncontrolled Diabetes Diabetes Mellitus, Glucocorticoid Excess, Thyrotoxicosis
II. Primary Risk Factors for Garden-Variety Calcium Oxalate Stones
   A. Family History
   B. Hyperoxaluria
   C. Inadequate Urine Volume
   D. Hyperuricosuria
   E. "Idiopathic" Hypercalciuria
      1. "Absorptive" Hypercalciuria
      2. "Renal" Hypercalciuria
      3. "Dietary" Hypercalciuria
   F. Multiple Risk Factors

Brief consideration will be given to the primary diseases producing secondary nephrolitihiasis; these made up only a small portion of a calcium oxalate stone population. The garden-variety stone--lacking a known primary etiology--will then be considered separately. Based primarily on the physical chemical properties described above, individual risk factors will be considered--much in the manner for which such variables as cigarette smoking, serum cholesterol, and hypertension are commonly evaluated in the case of coronary artery disease. Etiologies of "idiopathic" hypercalciuria will receive particular attention, with emphasis placed upon the importance of "absorptive" hypercalciuria and the newly-defined entity "dietary" hypercalciuria.

Primary Hyperparathyroidism

Although there will be little of novel interest to say regarding primary hyperparathyroidism, a number of basic points will be reemphasized. This disorder is an important primary disorder of renal stone disease. Indeed, some fifty per cent of hyperparathyroid patients have renal calculi as their presenting complaint. (Broadus, 1981) The key point meriting emphasis is that certain patients with primary hyperparathyroidism manifest disproportionate hypercalciuria vis-à-vis the fasting serum calcium concentration, and it is this subpopulation which is predominantly at risk for stones. The principal pathophysiological correlate explaining the disproportionate hypercalciuria is the circulatory concentration of $1,25\text{-}(OH)_2D$, so that the hypercalciuria is predominantly "absorptive" in nature. (Broadus, 1980, 1981)

Enteric Hyperoxaluria

Enteric hyperoxaluria has been considered as a distinct entity since 1972, following recognition that hyperoxaluria and a predisposition to nephrolithiasis were seen in a variety of gastrointestinal disorders, including Crohn's disease, nontropical sprue, chronic pancreatitis and biliary tract disease, blind loop syndrome, and following ileal resection or jejunoileal bypass, but not including ulcerative colitis. This study will echo the association between enteric hyperoxaluria and renal calculi, but will not explore this relatively minor cause of stone disease further. The pathophysiology is thought to involve a colonic hyperabsorption of dietary oxalate. The particular mechanism of this hyperabsorption has not been established. By predisposing the urine to oversaturation, enteric hyperoxaluria is thought to stimulate calcium oxalate stone formation. (Smith, 1980)

Renal Tubular Acidosis

These stones are significantly composed of calcium phosphate and were considered in a previous section.

Sarcoidosis

Hypercalciuria has been noted in approximately forty per cent of patients with sarcoidosis, and this disease has been associated with calcium oxalate stone formation. (Winnacker, 1968, Broadus, 1981) The hypercalciuria is a function of dietary calcium intake, renal function, bone resorption, and abnormal rates of conversion of 25-OH D to 1,25-$(OH)_2$D. (Papoulos, 1979) By promoting an oversaturated urine with respect to calcium, sarcoidosis can predispose to calcium oxalate stone formation. Diagnosis of sarcoidosis is made from radiographic, chemical, and biopsy evidence of the disease. This study will confirm that this disease is infrequently seen in a stone population. (Broadus, 1981)

Other Secondary Hypercalciurias

Other primary diseases have been suggested as predisposing patients to hypercalciuria and, rarely, nephrolithiasis, although they were not observed in this series. (Broadus, 1981) These diseases include "excess Vitamin D intake," immobilization, rapidly progressive osteoporosis, malignant osteolysis, medullary sponge kidney, uncontrolled diabetes mellitus, glucocorticoid excess, thyrotoxicosis, acromegaly, and furosemide administration. All have been variously associated with hypercalciuria, but their relationship to stone formation has been poorly studied.

Family History

Family history is strongly associated with this disease. No genetic markers have yet been identified, but family history confers a definite statistical risk. (Resnick, 1968) This study confirms the high rate of positive family history for renal stones among patients with renal stones.

Hyperoxaluria

As described in the section on physical chemistry, hyperoxaluria, theoretically, would predispose a patient to formation of calcium oxalate stones. Because urine oxalate was only studied systematically in patients suspected of having enteric hyperoxaluria, and not in the entire stone population, this study did not determine whether hyperoxaluria was a significant risk factor in patients with garden variety calcium oxalate stone disease.

Hypouresis

As calcium oxalate in normal urine just borders on the edge of oversaturation, hypouresis is yet another risk factor that can play a critical role in pathogenesis. An inadequate urine output might be sufficient cause for calcium oxalate becoming oversaturated in urine, compelling calcium oxalate crystal formation. (Pak, 1980) The common prevalence of inadequate fluid intake and resulting low urinary output in Israeli settlement towns of the 1950's was, indeed, suggested as the cause of the high incidence of renal stone disease in that country. (Frank, 1959) In the present study, an "inadequate" urine was considered to be less than one liter per day.

Hyperuricosuria

A risk factor that will be emphasized is hyperuricosuria. The entity of hyperuricosuric calcium oxalate nephrolithiasis was initially recognized in the 1970's. (Coe, 1973, Coe, Kidney International, 1978, Coe, Nephrolithiasis, 1978). A reliable mechanism for this process has not yet been established, although there have been reports that epitaxy might play a role. According to this theory, when different crystals types share a similar lattice structure, saturation with one solute type might induce heterogeneous nucleation (i.e. precipitation) and/or crystal growth of another type of solute. Since calcium oxalate, uric acid, and monosodium urate crystals have been reported to share similar lattice structures, this might be the mechanism by which

hyperuricosuria favors production of calcium oxalate stones. (Lonsdale, 1968) Details of purine metabolism were considered earlier under Uric Acid Stones. What makes assessing this risk factor especially difficult is that statistically precise limits for normal uric acid excretion have not been established. Because intestinal absorption of purines is not regulated, hyperuricosuria is frequently a simple function of purine intake. This study employed the upper normal limit recommended by others, even though it was recognized that these limits were not statistically based. These criteria defined hyperuricosuria as uric acid excretion of more than 800 mg per day in males and 750 mg per day in females. (Coe, Kidney International, 1978). Three potential mechanisms for hyperuricosuria in patients with oxalate stone disease are: 1) endogenous uric acid overproduction, 2) purine gluttony, and 3) increased fractional excretion of uric acid. (Broadus, 1978) This study will echo that little support for the third hypothesis exists. That a majority of patients with hyperuricosuria are normouricemic suggests that two subpopulations might exist, one of overproducers, the other of purine gluttons. Clearly, exogenous purines would influence uric acid excretion in both subpopulations, and the line between them is thin.

"Idiopathic" Hypercalciuria

The risk factor to which particular attention will be paid is hypercalciuria. An association between hypercalciuria and calcium stone formation has been known since 1939. (Flocks, 1939) Unfortunately, delineating the nature of the hypercalciuria has progressed slowly. Since 1958, the renal stone literature has contended with the term "idiopathic hypercalciuria" to describe those hypercalciuric patients for whom no primary disease could readily be identified as causing their hypercalciuria. These patients were thought to have normocalcemic hypercalciuria and a tendency to hypophosphatemia. They were noted to have increased intestinal calcium absorption, which, at the time, was considered secondary to a "renal leak" of calcium. (Henneman, 1958) In the ensuing quarter-century, debate has raged over the mechanisms and frequencies of subgroups of "absorptive," "resorptive," and "renal" hypercalciurias that were thought to comprise the idiopathic hypercalciurias. (Broadus, 1984).This study will emphasize the prevalence of the entity known as "absorptive hypercalciuria."

In practice "hypercalciuria" is difficult to define in a meaningful way because there are so many dietary influences on calcium excretion. On a "free" or undefined diet, calcium excretion can be increased by dietary protein, sodium, and carbohydrate, and decreased by dietary oxalate and phosphorus. Dietary calcium itself can profoundly increase urinary calcium, especially in renal stone formers. (Peacock, 1967, Lemann, 1979)

A "hypercalciuric" patient was defined in this study as one who met at least one of the following criteria: On either or both of the protocol diets (see Appendix Two), they had 1) a calcium excretion rate of greater than 250 mg per day in females; 2) greater than 300 mg per day in males; or 3) greater than 4 mg per kg per day in either

sex. These limits are consistent with those recommended by most investigators within the United States. (Broadus, 1981)

The most common subtype of idiopathic hypercalciuria associated with the "typical oxalate stone" is absorptive hypercalciuria. As currently understood, this disease involves increased circulating levels of $1,25\text{-}(OH)_2D$, leading to intestinal hyperabsorption of calcium. These patients have an increased gut absorption of calcium that presents the normal kidney with an increased load of calcium, which is then excreted, causing hypercalciuria. (Coe, Nephrolithiasis, 1978, Broadus, 1981, Broadus, 1984) This study examined one proposed mechanism for absorptive hypercalciuria, involving a primary renal tubular phosphate leak. (Lemann, 1980) According to theory, for which this study found no support, the phosphate leak leads to a reduction in TmP/GFR and serum phosphate concentrations and secondary increases in $1,25\text{-}(OH)_2D$ and intestinal calcium absorption. A full discussion of the phosphate leak hypothesis is beyond the scope of this thesis.

Renal hypercalciuria is thought to involve a primary defect in renal tubular calcium reabsorption. The tubular calcium losses lead to secondary hyperparathyroidism, the theory goes, stimulating $1,25\text{-}(OH)_2D$ production, calcium absorption, and reducing TmP/GFR and serum phosphorous. (Broadus, 1979, Broadus, 1981). This study found no evidence of such a mechanism.

Patients with so-called "idiopathic" hypercalciuria have been noted to increase their urine excretion of calcium markedly in response to increasing dietary calcium from a low-normal to a high-normal level. In contrast, normal subjects show a minimal increase under these conditions. (Broadus, 1979) In this series, it was presumed that hypercalciuric patients would manifest a greater degree of hypercalciuria on the fixed (1000 mg) calcium diet than on the "free" diet sample (typically with a lower in-

take of calcium). As will be seen, a substantial minority of patients did not display such a pattern. Rather, they displayed more marked hypercalciuria on the "free" diet than on the fixed high-normal calcium diet, even though, on the average, the calcium intake on the fixed diet was some one-third higher than that on the "free" diet. Most of this subset of patients did not have an identifiable metabolic abnormality on detailed testing. It follows that dietary factors other than calcium must have influenced the results for calcium excretion on the "free" diet, and the term "Dietary Hypercalciuria" is introduced in connection with these patients. The patients considered in this category were those who displayed hypercalciuria on one of the protocol diets and whose calcium excretion was more than 50 mg/day higher on the "free" diet as compared with the fixed 1000-mg calcium diet, along with those patients who, paradoxically, were hypercalciuric on both diets, but whose performance on a calcium tolerance test indicated that they did not have absorptive hypercalciuria. Together these two subgroups were considered as one cohort. Because such variables as dietary calcium, phosphorus, protein, and sodium are not set in the "free" diet, while they are regulated in the fixed diet, the hypothesis that one or more of these dietary factors might influence the result on the free diet urine calcium was considered.

Diagnosis of hypercalciuric etiologies was made through measurements of fasting calcium excretion, 24-hour calcium excretion, total serum calcium, ionized serum calcium, serum immunoreactive PTH, nephrogenous cAMP, and total cAMP excretion, as detailed in the methods sections below and in Appendix Two.

## METHODS

The Stone Clinic: The Yale-New Haven Medical Center Renal Stone Clinic is a weekly outpatient referral clinic in New Haven, Connecticut. Since its inception in

1977, the clinic has been conducted by a minimum of three internists, a nurse, and a dietician.

The Patient Population: Although a small number of patients were self-referred to the clinic, the vast majority were either referred by a urologist, a general practitioner, or an internist. The clinic has been in continuous operation since 1977. This study examines the historical record of the first 279 clinic patients who had been evaluated as of October 1982.

Screening Schedule: The evaluation screen at the stone clinic was established to take place over two clinic visits. The purpose of the initial visit was to determine all historical, radiological, and physical exam parameters relating to the patient's stone disease, to obtain serum and urine specimens reflecting the "free" diet, and to instruct the patient on the nature of the fixed diet, from which urine calcium was quantified upon the second clinic visit. The purpose of the second clinic visit was to inform the patient of the results of tests conducted on the first visit and to plan future tests and/or therapy. In the case of unexplained hypercalciuria, this would involve scheduling a calcium tolerance test. If radiological information available at the first visit was unsatisfactory, a set of KUB and oblique abdominal films was scheduled for the second visit. Therapy might commence with dietary counseling and/or medication.

Initial Evaluation: Prior to arrival at the clinic for his first appointment, each patient was sent a copy of a "First Renal Stone Clinic Visit" form. (See Appendix Two) Along with the form is sent a collapsible 24-hour urine container and instructions for collecting a one-day sample. Each patient was instructed to arrive to the clinic in a fasting state. On admission to the clinic, a complete history and physical examination was performed on each patient. Particular attention was paid to the history of

stone events, dietary, and associated factors as noted on the forms in Appendix Two. When permission was granted to study a patient's family history, a detailed pedigree was prepared for each first-degree relative of the affected patient. Patients with at least one first-degree relative with a reported history of passage of a renal calculus were considered as having a positive family history. A detailed, quantitative, dietary history was obtained by a trained nutritionist, using the diet history form in Appendix Two. This history corresponded to the day of the "free" urine collection.

Radiological evaluation: An intravenous pyelogram (IVP) from within one year of intake was examined on every patient, whenever possible. Particular attention was paid to assessing anatomical abnormalities predisposing to stone formation and determination of the quantity and quality of any stones present. Flat abdominal and oblique films were obtained whenever old films were insufficient for reliable diagnosis of stone number, type, and/or location.

Laboratory evaluation: Results of previous stone analyses were examined and, whenever possible, a representative recent stone was sent for crystallographic analysis. At the patient's inital clinic visit, fasting blood levels of calcium, phosphorus, bicarbonate, chloride, creatinine, and uric acid were determined. The inital twenty-four hour urine specimen on a "free" or undefined diet (as noted on the diet history form) was analyzed quantitatively for creatinine, calcium, sodium, phosphorus, magnesium, uric acid, and TmP/GFR. In many cases the fractional excretion of uric acid was also determined. Urine volumes were also noted and the creatinine quantitated to ensure completeness of the collection. A clean-catch, spot, fasting urine was also obtained for culture and for pH determination by nitrazine paper or pH meter. In all cases a cystine screen (nitroprusside) was performed on this specimen. If the initial urinary pH was greater than 5.5, the patient was given nitrazine paper

for recording serial urinary pH values in order to document that the urine could be acidified to a pH of less than 5.5. The average pH of the first eighteen consecutive urine samples was designated as the "mean pH." The presence and degree of hypercalciuria were evaluated by instructing patients to collect two twenty-four-hour urine samples on a "fixed" or defined 1000-mg calcium diet. For this regimen (see patient form in Appendix Two) patients were instructed by the dietician to limit their protein intake to approximately one gram per kg of body weight per day, to limit their sodium intake to approximately one hundred milliequivalents per day, to eliminate dairy products, and to supplement the diet with calcium gluconate tablets, two grams, three times daily with meals. The net calcium intake on the fixed diet was approximately 1 gram per day, and the urine collections were obtained after at least one full day on the diet. Patients who were hypercalciuric on either diet or both and for whom no primary cause for the hypercalciuria was identified were then evaluated with an "Oral Calcium Tolerance Test" described in Appendix Two. (Broadus, 1978) The calcemic response (in normal individuals it is usually less than 0.4 mg/dL) is an index of calcium "tolerance." The calciuric response served as an index of intestinal calcium absorption. Induced changes in nephrogenous cAMP or total cAMP excretion served to indicate parathyroid suppressibility, as it is the best clinical means of measuring circulating parathyroid hormone activity. (Broadus, 1981) Absorptive hypercalciuria was diagnosed in patients who met the strict criteria described in Appendix Two. (Broadus, 1984).

RESULTS

The stone population was made up of 169 males and 60 females. This sex distribution was almost identical to that reported (70:30) in a previous study of a large group of stone patients. (Prince, 1960) The mean age of the stone clinic patients at the time of their first stone episode was 34 years. (See Figure One) The mean frequency of previous stone episodes since the first stone episode among stone patients was two per year. (See Figure Two) Two patients had sarcoidosis, three had cystinuria, four had renal tubular acidosis, eight had enteric hyperoxaluria, and ten had primary hyperparathyroidism. Of those patients without a known primary disease explaining the formation of their calculi, six had uric acid stones, nine had magnesium ammonium phosphate stones, fifteen had calcium phosphate stones, and one hundred eighty had calcium oxalate or mixed calcium stones. Eleven patients had more than one type of stone. Detailed averages of urinary excretion rates appear in Appendix One.

FIGURE 1:

Distribution of Ages At First Stone Episode
x-axis: age (years)...y-axis: number of patients

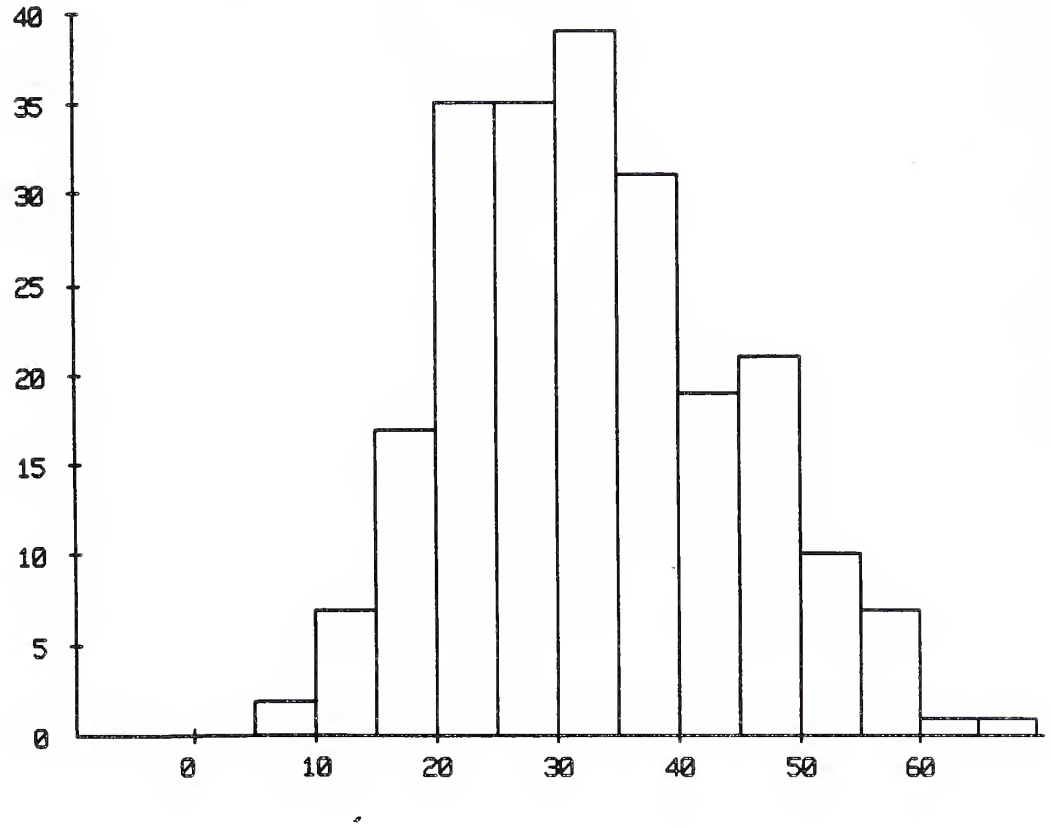
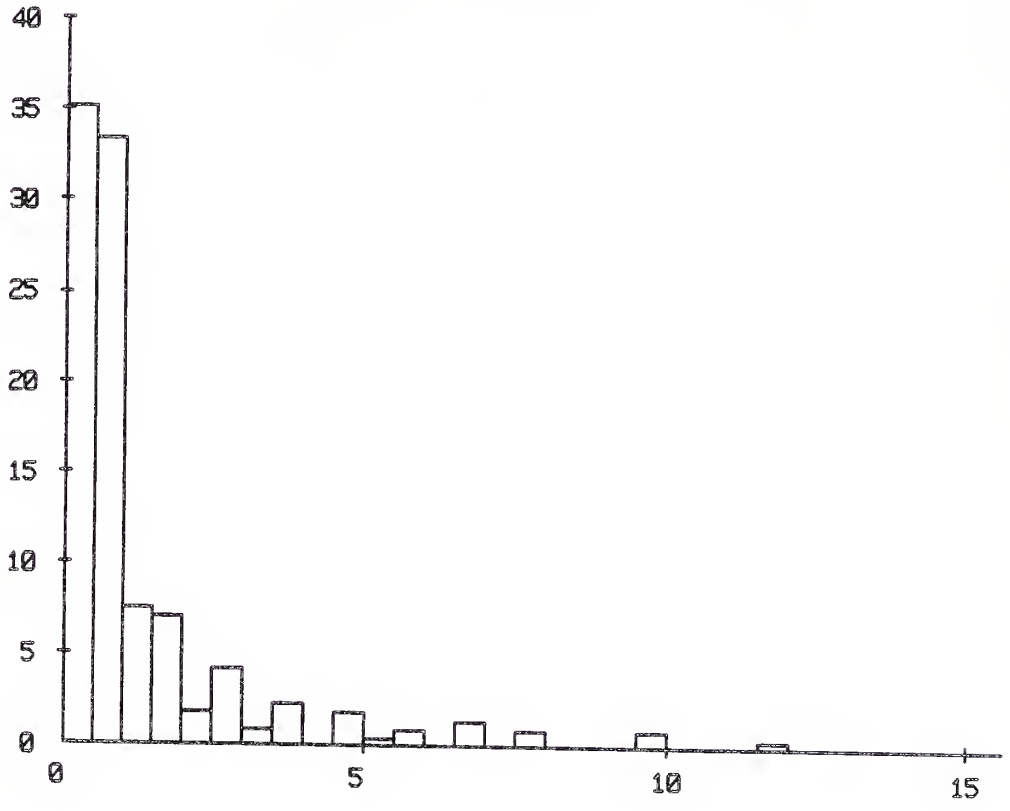


FIGURE 2:

Frequency Distribution of Mean Annual Stone Episodes
x-axis: episodes per year...y-axis: percentage of patients
One patient's stone frequency fell above the range depicted on the table below.



MAP Stones

Among the nine patients who developed MAP stones, three (33%) had a positive family history for renal stone disease. Although the organism count was higher in this group ($\mu$=45,600) than in the remainder of the stone patients studied ($\mu$=9,900, S.D.=74,000, N=195), the difference was not large enough to be significant (p=.074). A positive culture was noted in six of the eight patients for whom a culture result was available. In this group of patients, 50% had a bacteriuria count of greater than 40,000 per milliliter, while only 6% of the remaining stone patients had bacteriuria greater than 40,000 per milliliter. Five of the eight patients with culture results available had a colony count of less than one hundred thousand per milliliter. (See Figures Three and Four) Among the cases where a presumably causative organism could be identified, Proteus mirabilis was the dominant organism in four cases, Pseudomonas aeruginosa in one, and Enterococcus in one more.

FIGURE 3:

Distribution of Organism Count in MAP Stone Patients

x-axis: organisms/ml...y-axis: number of patients whose colony count equalled the value on the x-axis at the left side of the bar

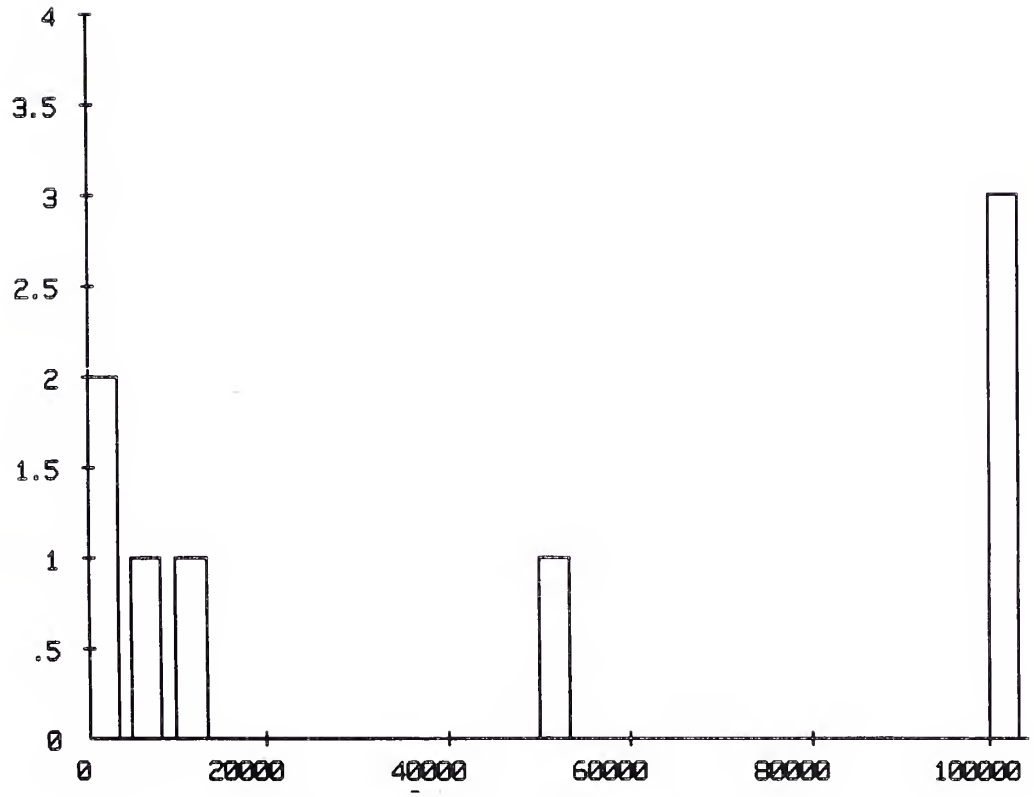
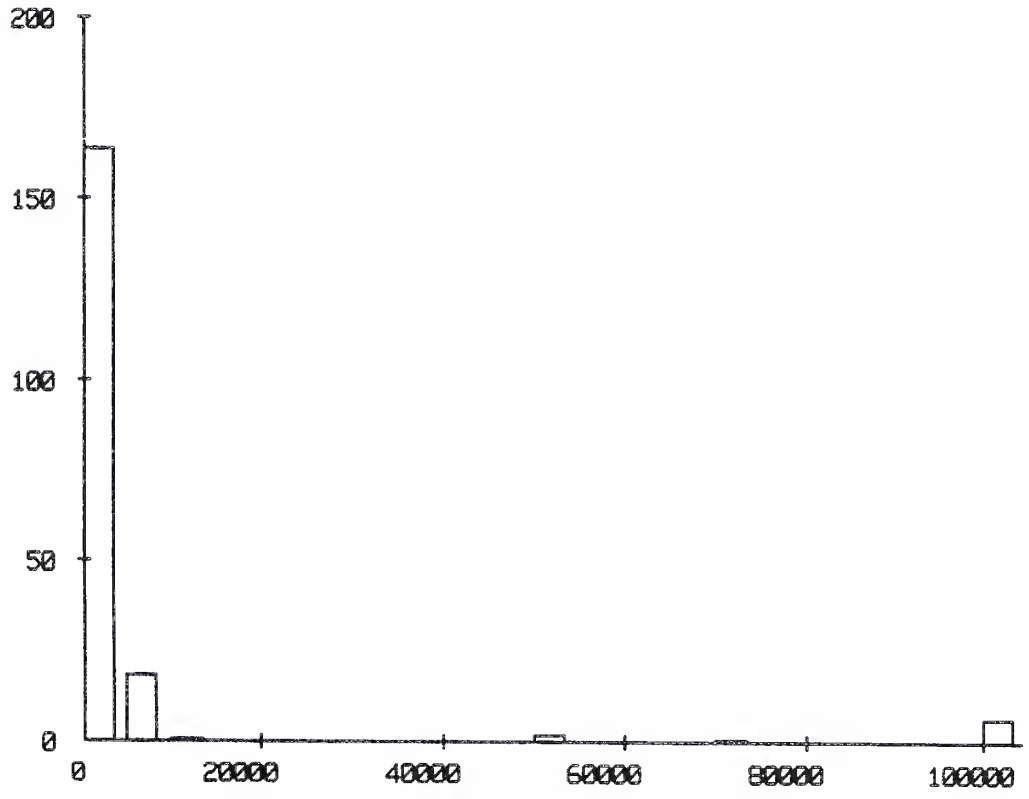


FIGURE 4:

Distribution of Organism Count in non-MAP Stone Patients

x-axis: organisms/ml...y-axis: number of patients whose colony count equalled the value on the x-axis at the left side of the bar

One patient's colony count was above the range depicted on the chart below.



Among these nine patients, five had "urinary tract infection" as their primary diagnosis predisposing them to renal calculus formation. One had medullary sponge kidney--presumably having an anatomical and functional urinary tract dysfunction predisposing to urinary tract infection. One had hypouresis as a risk factor, as well as a history of urinary tract infections (documented with repeated urinary cultures), thought secondary to chronic nephrolithiasis. One patient had a history of antacid abuse and another was hyperuricosuric, both of which were thought to have induced a "metabolic" stone formation and undocumented secondary urinary tract infection. The TmP/GFR of the MAP stone population ($\mu$=2.4) was significantly less (p=.001) than that observed in the remainder of the stone population ($\mu$=3.1, S.D.=0.7, N=194).

Uric Acid Stones

As a group, the uric acid stone population had a significantly (p=.003) lower urine volume ($\mu$=1000 ml) than the rest of the stone patients ($\mu$=1623 ml, S.D.=811, N=223). Although 50% of this group had urine volumes less than 1000 ml, only 18% (40 of 223) of non-uric acid stone formers had such low urine volumes. At this level of urine output, hypouresis would be an appropriate term for describing their state. Dietary purine intake per kg body weight ($\mu$=1.92 mg/kg, S.D.=1.09, N=6) was not significantly different than that observed among the rest of the stone population ($\mu$=1.70 mg/kg, S.D.=1.28, N=211). Three of the six patients also had a history of oxalate stones; two of the six had hyperuricosuria; one had gout; and one had Crohn's disease. When compared to the rest of the stone population, the uric acid stone formers had no significant difference (p>.05) in their serum or urinary uric acid levels, or in their Fractional Excretion of Uric Acid. The mean urinary pH measured for two of the six patients with uric acid stones, was approximately the same as that obtained in the non-uric acid stone population ($\mu$=5.8, S.D.=0.7, N=107). There were no

known patients in this uric acid group who had any of the rare inborn error of metabolism diseases that can cause uric acid stones.

Cystine Stones

All three of the patients who developed cystine stones in this series had a diagnosis of cystinuria. Two of the patients (brothers) had a family history of stone disease. The average age of onset of stone episodes was eighteen years. Daily urine volumes averaged 1160 ml, and urine cystine averaged 811 mg/day. All of the urine cystine concentrations ($\mu$=648 mg/L) exceeded the maximum solubility (300 mg/L) of cystine in urine.

Calcium Phosphate Stones

A total of seventeen patients formed pure or predominantly calcium phosphate stones. Two of these had renal tubular acidosis. Of the remaining fifteen patients without a "primary" disease process leading to their formation of phosphate calculi, two had a history of chronic antacid ingestion, and another had a history of regular acetazolamide ingestion. As such, there were a total of twelve patients without a readily identifiable source of an alkaline urine that would predispose to calcium phosphate stone formation. The mean urinary pH in the seven of these twelve patients in whom "mean urinary pH" was determined ($\mu$=6.1) was higher ($p=.002$) than that observed in the rest of the studied population ($\mu$=5.8, S.D.=0.7, N=102). There was no significant difference ($p>.05$) between the TmP/GFR in these patients ($\mu$=2.9) and the rest of the stone population ($\mu$=3.1, S.D.=0.7, N=193). Nor was there any significant difference between the serum chloride, serum bicarbonate, or lowest recorded urinary pH of these twelve calcium phosphate stone patients and the remainder of the stone population.

Calcium Oxalate Stones

With a distribution of 151 males and 47 females in this series having oxalate stones, it becomes clear that this type of stone disease has a predilection ($p<.05$) for males (Chi Square Value>3.841). Although oxalate stone disease is a curse of industrialized nations, it is the male population, especially, who suffer from the curse.

Renal Tubular Acidosis

Of the 198 patients with calcium oxalate stones, only one was diagnosed as having renal tubular acidosis.

Sarcoidosis

Two patients in this series had calcium oxalate stones associated with sarcoidosis. Of note was that their serum calcium averaged 10.2 mg/dL and that their 24-hour calcium excretion on the fixed diet averaged 5.2 mg/kg Wt.

Enteric Hyperoxaluria

Eight patients in the calcium oxalate-mixed calcium stone group had enteric hyperoxaluria. Not suprisingly, they were noteworthy for having a 24-hour urine oxalate ($\mu=74$, $N=5$) that was significantly ($p=.035$) greater than that observed among the other members of the stone population whose urinary oxalate values were quantified ($\mu=52$, $N=26$). 80% of the patients in this group had a urinary oxalate of greater than 55 mg/day. Only 27% (7 of 26) of the remaining stone patients for whom urinary oxalate was examined had such high urinary oxalate levels.

Primary Hyperparathyroidism

The ten patients with primary hyperparathyroidism in this series included three males and seven females. This three to seven sexual distribution is similar to that reported in previous studies of a large group of stone patients. (Broadus, 1981) The serum calcium in this population was clearly above normal ($\mu=11.2$ mg/dL, S.D.=1.1,

N=8). The urinary calcium on the fixed diet ($\mu$=5.1 mg/kg, S.D.=1.9, N=8) was significantly higher ($p<.001$) than that observed in the remainder of the stone population ($\mu$=3.2 mg/kg, S.D.=1.4, N=214). 50% of the patients in this group had a fixed diet urinary calcium greater than 4.8 mg/kg of body weight. Only 14% (31 of 214) of the remainder of the stone population had such a degree of hypercalciuria.

"Garden-Variety Stone Disease"

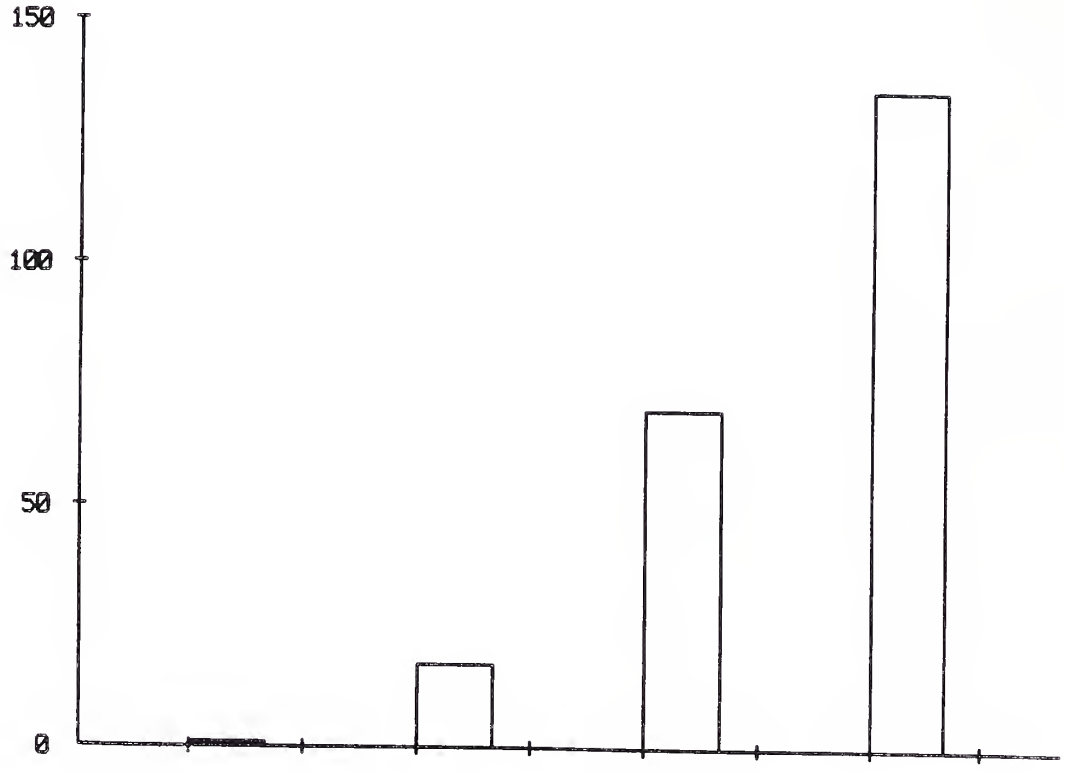
Hypouresis, manifested by a urine volume of less than one liter per day, was observed in 36 of 179 patients (20%). Hyperuricosuria was manifest in 57 of 178 patients (32%). (The urinary uric acid was not available in the case of one patient.) Hypercalciuria (measured on either or both of the "free" and regulated diets) was observed in 81 of 179 patients (45%).

From the risk factor perspective, 136 (87%) of the 156 "garden-variety" oxalate stone patients for whom family histories were available manifested at least one of the risk factors of positive family history (stone disease in at least one first degree relative), hypouresis, hyperuricosuria, or hypercalciuria, with only some 13% having no identifiable risk factors within these categories. (See Figure Five) Of note was the fact that positive family history for renal stone disease was seen in patients manifesting each of the three treatable risk factors of hypouresis, hyperuricosuria, and hypercalciuria. Of those patients for whom a family history was obtained in this category, 12 of 28 low volume patients (43%), 22 of 42 hyperuricosurics (52%), and 32 of 69 hypercalciurics (46%) had at least one first degree relative with a history of renal calculi. (See Figure Six)

FIGURE 5:

Cumulative Frequency Distribution of Patients with Specific Numbers of Identifiable Risk Factors (Positive Family History, Low Urine Volume, Hyperuricosuria, Hypercalciuria) among 156 Patients with "Garden-Variety" Calcium Oxalate and Mixed Oxalate Stones

y-axis: number of patients

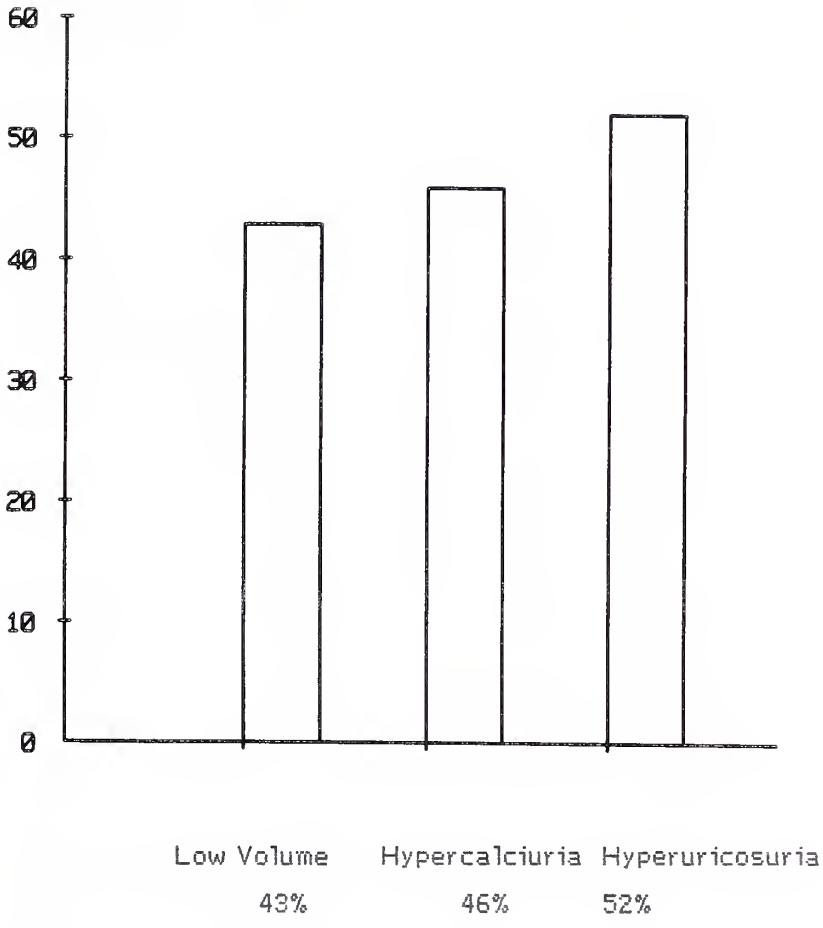



| # of Risk Factors | 4 | 3-4 | 2-4 | 1-4 |
|---|---|---|---|---|
| # of pts | 1 | 17 | 70 | 136 |
| % of pts | 1 | 11 | 45 | 87 |

FIGURE 6:

Positive Family History Manifested among Patients with Treatable Risk Factors for Renal Stone Disease

y-axis: per cent of patients with indicated risk factor who have positive family histories



Looking at treatable risk factors alone (i.e. hypouresis, hyperuricosuria, and hypercalciuria), of the 179 patients with "garden-variety" stone disease, 44 had no identifiable risk factors, 98 (55%) had one identifiable risk factor, 35 (20%) had two identifiable risk factors, and 2 (1%) were positive for all three risk factors. There was no correlation ($p>.05$) between the number of identifiable risk factors that the patients manifested and the mean number of renal stone episodes that they experienced per year.

Among the 36 patients with a low urine volume, the average age of presentation at the stone clinic was 32. 26 (72%) were males and 10 (28%) were females. 6 (17%) of the 36 had coincident hyperuricosuria, and 6 (17%) had coincident hypercalciuria.

To understand the nature of hyperuricosuria seen in stone patients, hyperuricosurics from the "garden-variety" stone population were analyzed as a separate group. This group was made up of 52 males and 5 females. 26 (46%) were hyperuricemic (as defined by a serum uric acid value greater than 7.0 mg/dL in a male or greater than 6.0 mg/dL in a female). (Wyngaarden, 1976) The fractional excretion of Uric Acid (F.E.U.A.) ($\mu=.076$) among this group was not significantly greater ($p=.109$) than the value observed in the remainder of the stone population in whom fractional excretion was determined ($\mu=.063$, S.D.=.031, N=23). Serum uric acid ($\mu=6.8$ mg/dL) was higher ($p=.001$) in this group of patients than in all other patients that were studied ($\mu=6.0$ mg/dL, S.D.=1.7, N=170). 63% of this group had a serum uric acid level greater than 6.2 mg/dL, while only 42% (72 of 170) of the remaining patients had such a high level. Dietary purine intake was also higher ($p=.008$) in this group of patients ($\mu=156$ mg) than in all of the other stone patients studied ($\mu=114$ mg, S.D.=80, N=161). 55% of this group had a dietary purine intake greater than 128 mg/day, while only 35% (56 of 161) had such a high intake. Of note is the fact that among the entire stone clinic popula-

tion, a positive correlation existed between Dietary Purine/kg Wt and Urinary Uric Acid/kg Wt, (N=221, r=.186, p=.006).

To examine the nature of the hypercalciuria in the patients who were hypercalciuric on one or both diets, the 81 oxalate stone patients from the entire stone population who fulfilled these criteria were examined as one group. This group excluded patients with primary hyperparathyroidism, renal tubular acidosis, sarcoidosis, and enteric hyperoxaluria. 56 of these 81 (69%) were found to have absorptive hypercalciuria, 14 (17%) had normal calcium tolerance tests, and 11 (12%) were not fully evaluated, as noted in the following table:

| HYPERCALCIURIC? | FREE DIET only | FIXED DIET only | BOTH DIETS | TOTAL |
|---|---|---|---|---|
| Absorptive Hypercalciuria | 5 | 22 | 29 | 56 |
| Normal Calcium Tol. Test | 4 | 7 | 3 | 14 |
| No Work-Up | 5 | 0 | 6 | 11 |
| TOTAL | 14 | 29 | 38 | 81 |

There was no significant difference ($p>.05$) between the TmP/GFR of the absorptive hypercalciurics ($\mu=3.1$) and that of the non-hypercalciurics seen in the stone clinic ($\mu=3.0$, S.D.=0.7, N=87). Of note, there was a strong correlation ($p<.001$) between the daily phosphorous intake per kg of body weight and the daily urinary phosphorous per kg of body weight output (r=.274). (See Figure Seven) In addition, there was a strong correlation ($p<.001$) among the entire stone population between serum phosphate and TmP/GFR (r=.656). Excluding two patients in the series with creatinine levels greater than 1.5, the correlation remains strong ($p<.001$) and the r

value for the serum phosphate vs TmP/GFR correlation increases to .760. (See Figure Eight)

FIGURE 7:

Linear Regression Superimposed upon Scatterplot of Dietary Phosphorus vs. Urinary Phosphorus

x-axis: dietary phosphorus (mg/kg Wt/day)...y-axis: urinary phosphorus (mg/kg Wt/day)

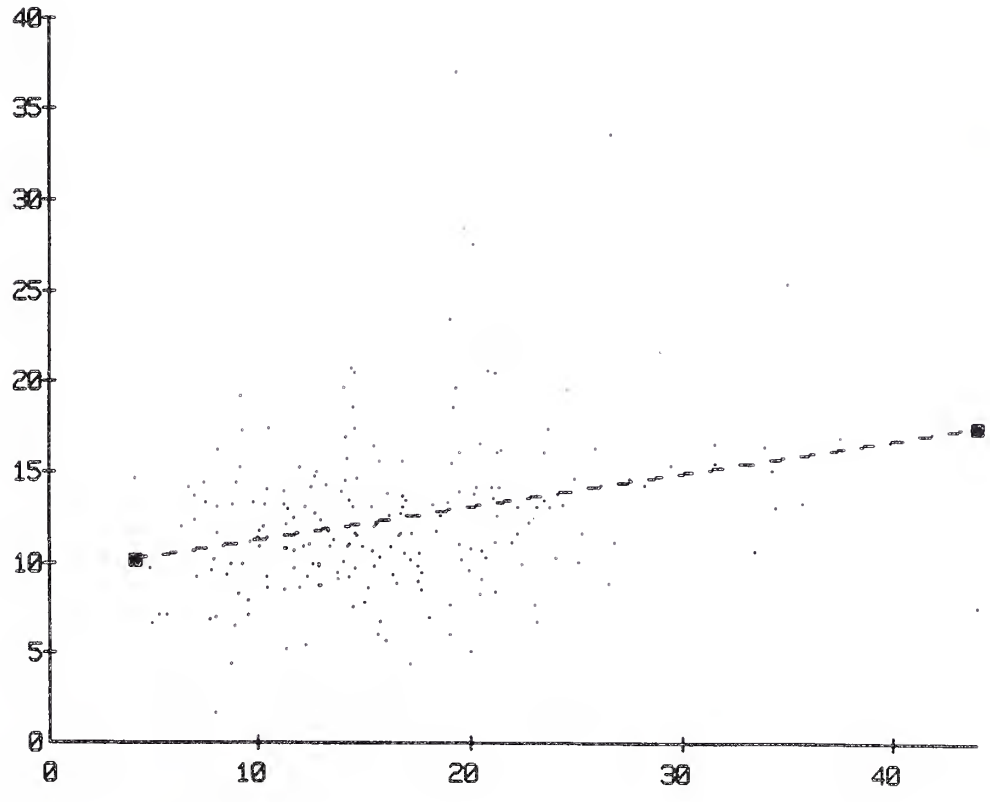
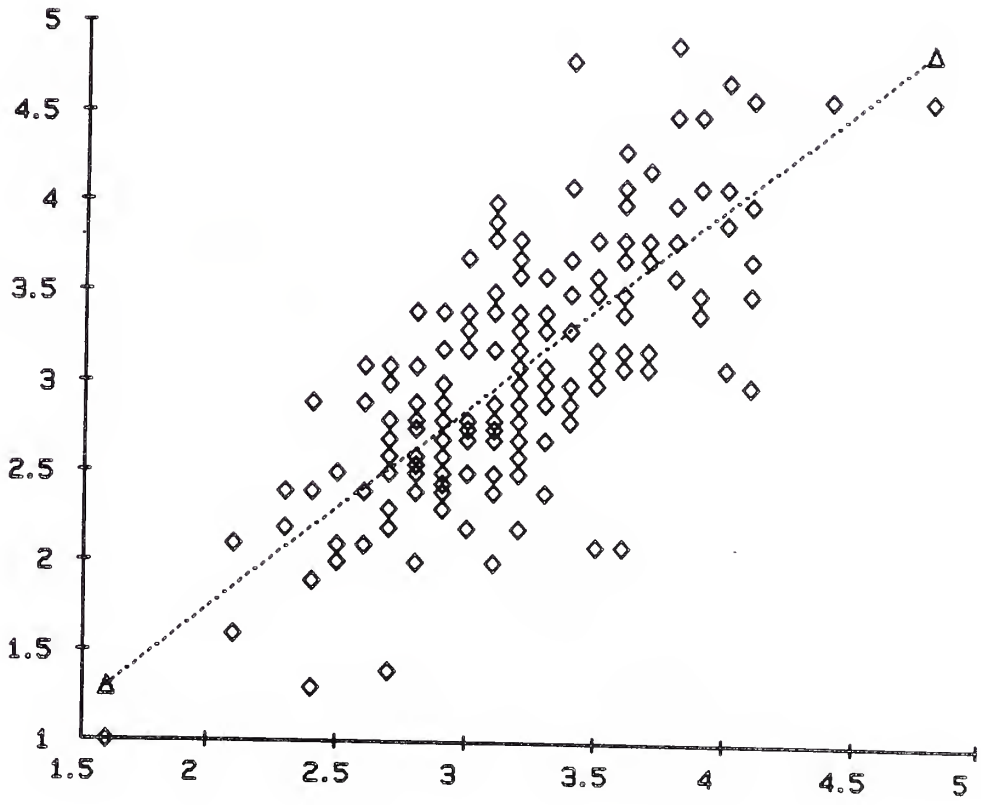


FIGURE 8:

Linear Regression Superimposed upon Scatterplot of Serum Phosphate vs. TmP/GFR

x-axis: serum phosphate (mg/dl)...y-axis: tmp/gfr

Two patients with serum creatinine greater than 1.5 mg/dl are excluded from below

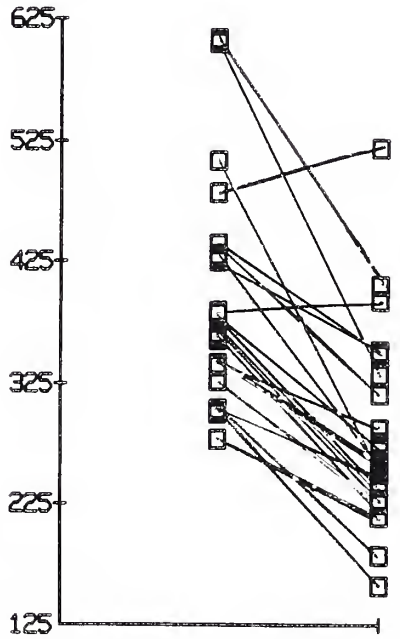


To examine the possibility that some patients were sensitive to dietary factors that might have promoted hypercalciuria, a subgroup of patients was examined in particular. The 23 patients who comprised this group were those hypercalciuric oxalate stone patients who did not have a primary stone-predisposing process, and who met at least one of the following conditions: 1) their urine calcium excretion on the free diet was over 50 mg higher than on the fixed intake diet (N=21), or 2) they were hypercalciuric on both diets, but a calcium tolerance test did not show evidence of absorptive hypercalciuria (N=3). The striking average decrease in calcium excretion in going from a low-normal calcium "free" diet to a high-normal 1000-mg defined diet may be easily appreciated in visual terms. (See Figure Nine)

FIGURE 9:

Urinary Calcium on a Low-Normal Calcium Diet vs. a High-Normal Calcium Diet in a Population of "Dietary Hypercalciurics"

x-axis: low-normal diet on lt, high-normal on rt...y-axis: urinary calcium (mg/day)

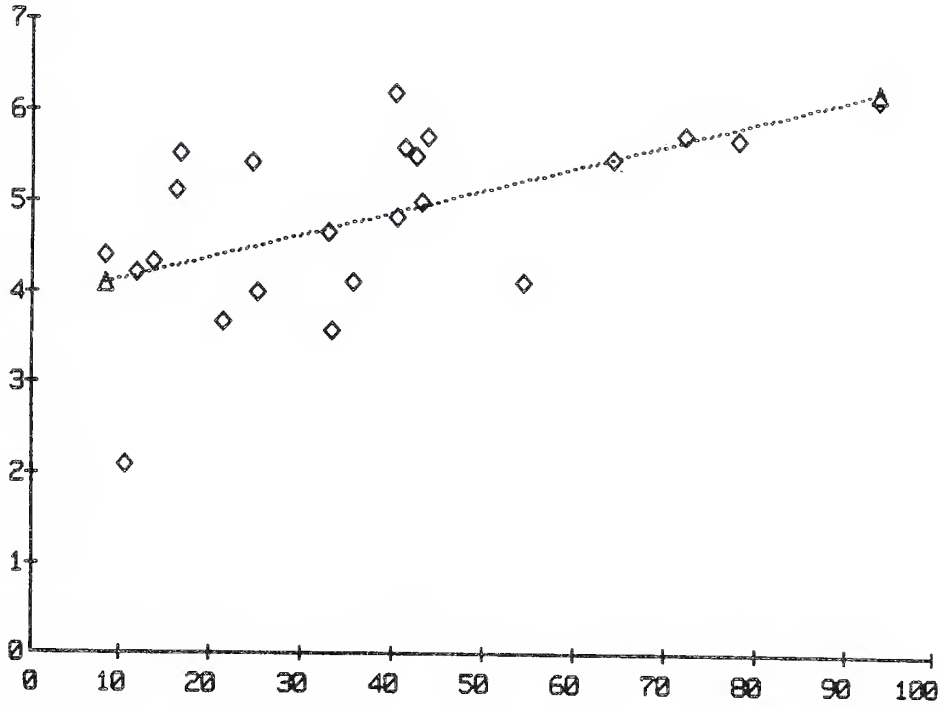


In this group, there was no correlation between dietary oxalate, phosphorus, purine, or protein intake ($p>.05$) and urinary calcium excretion. Dietary sodium intake per kilogram body weight, however, was found to correlate ($r=.576$, $p=.004$, $N=23$) with urine calcium excretion per kilogram body weight on the "free" diet. (See Figure Ten)

FIGURE 10:

Linear Regression Superimposed upon Scatterplot of Dietary Sodium vs. Urinary Calcium on Low-Normal Calcium Diet

x-axis: dietary sodium (mg/kg weight/day)...y-axis: urinary calcium on "free diet" (mg/kg weight/day)

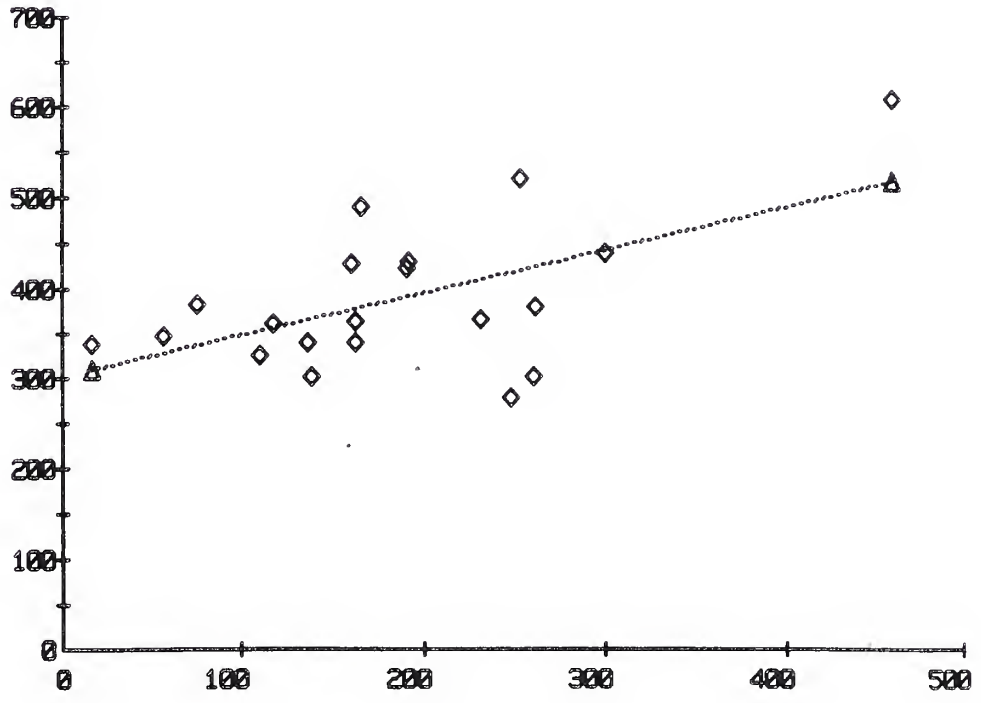


Urinary sodium excretion also correlated (r=.570, p=.009) with free diet urine calcium for the twenty patients among the twenty-three for whom a 24-hour urine sodium level was available. (See Figure Eleven)

FIGURE 11:

Linear Regression Superimposed upon Scatterplot of Urinary Sodium vs. Urinary Calcium on Low-Normal Calcium Diet

x-axis: urinary sodium (mg/day)...y-axis: urinary calcium on "free diet" (mg/day)

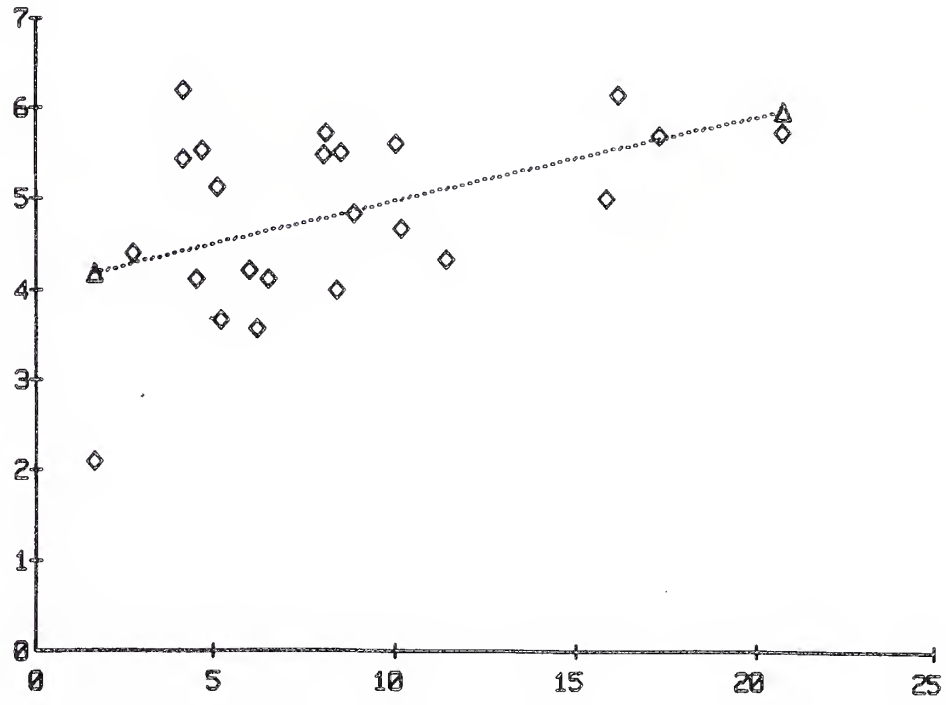


Finally, dietary calcium intake per kilogram body weight in these twenty-three patients was also found to correlate (r=.471,p=.023) with urine calcium excretion per kilogram body weight on the "free" diet. (See Figure Twelve) Of note, in this population of "dietary hypercalciurics" the good correlation between sodium (intake and output) and urinary calcium on the "free" diet was stronger than that between calcium intake and urinary calcium.

FIGURE 12:

Linear Regression Superimposed upon Scatterplot of Dietary Calcium vs. Urinary Calcium on Low-Normal Calcium Diet

x-axis: dietary calcium (mg/kg Wt/day)...y-axis: urinary calcium on "free diet" (mg/kg Wt/day)



## DISCUSSION

There are clear limits to the usefulness of the data presented in this study. Because the renal stone clinic operates as a referral center, the population that it serves is likely to be somewhat skewed from the "average" population of stone patients. As such, the patients who became part of its data base were more likely to represent, on the average, apparently greater degrees of stone pathology than patients treated solely by their primary physician.

### Cystine Stones

Treatment of cystinuria and prevention of cystine calculi formation centers on monitoring the cystine excretion rate. Since in cystine stone patients that rate is generally higher than the maximum solubility of cytine (300 mg/L) at physiological pH, a primary mode of therapy is reduction of the cystine concentration in urine to below the 300 mg/L level. A tolerable first-line approach would be forced hydration. If water alone is insufficient, then alkalinization of the urine may be attempted, as alkalinization of the urine to a pH of greater than 7.5 can double cystine solubility. A concern, of course, with alkalinization is that precipitation of calcium phosphate stones may be enhanced. Patients for whom these conservative measures are not fully effective may also be placed upon a cystine solubilizing drug such as D-Penicillamine. (Dahlberg, 1977) Unfortunately, this agent is quite toxic.

### MAP Stones

Urease produces the physico-chemical conditions necessary for urine supersaturation with magnesium ammonium phosphate and the vast majority of *Proteus* isolates are urease-positive. In this series, as in previous ones, the occurrence of *Proteus* species as the primary organism associated with the magnesium ammonium phosphate stone has obtained.

An important point to be noted is that the majority of stone patients with magnesium ammonium phosphate stones present with a urine culture colony count of less than 100,000 per milliliter. Examples of such low levels of organism counts have been reported previously out of the Mayo Clinic series. (Smith, 1976) Consequently, dismissal of a "negative" culture may cause a hasty clinician to ignore this potentially treatable and sometimes morbid form of renal stone disease. Because these stones may form secondarily to stasis or a "foreign body" focus caused by other stone types, an always essential first-step is to screen the patient for other risk factors and to treat those appropriately. Unfortunately, unless MAP stone material is completely removed or passed, it can serve as a nidus for stone recrudescence. Therefore, successful surgical therapy requires the complete removal of all stone material. Such procedures are often difficult and only partially successful. (Griffith, 1978) Other treatment regimes via diet or medication are still either experimental, impractical, or unavailable. (Broadus, 1981)

Uric Acid Stones

Because this group of patients had a highly significant (P=.003) lower urine volume than the rest of the stone population, weight is added to the hypothesis of some investigators that hypouresis is an independent risk factor for the formation of uric acid calculi specifically. What has not been explained is why uric acid stone formation should be especially sensitive to urine volume. (Broadus, 1981) The importance of hyperuricosuria as a risk factor was confirmed likewise. No evidence was found for differing fractional excretion of uric acid levels contributing to the formation of this type of stone. Because the average urine uric acid was 656 mg/L and uric acid solubility varies from about 100 mg/L at pH=5 to about 1500 mg/L at pH=7, the critical role that urinary pH can play in the formation of uric acid stones is evident.

In an acid urine, the stone patient would be much more likely to precipate his urinary uric acid than he would be in an alkaline urine. (Broadus, 1981) That one of the patients in this subgroup (17%) had Crohn's disease is meaningless in itself, but it does point out the increased association between inflammatory bowel disease and uric acid stone formation. (Broadus, 1981)

With the population of uric acid stone formers tending to underproduce urine chronically, forced hydration would seem to be the first step in rational treatment. For patients producing a persistently acid urine, alkalinization with sodium bicarbonate may also be attempted, although patient compliance is often poor. (Broadus, 1981) In patients with marked hyperuricosuria, or a severe history of stone disease, allopurinol has become the drug of choice in many uric acid stone patients. An analogue of hypoxanthine, it is a competitive inhibitor of xanthine oxidase, decreasing uric acid overproduction and excretion. (Holmes, 1980)

Calcium Phosphate Stones

As demonstrated by this study, an alkaline urine can be an important variable in the pathogenesis of calcium phosphate stones. That the difference in urine alkalinity holds up even when an obvious source of an alkaline urine factored out suggests the importance of the association of an alkaline urine and "idiopathic" calcium phosphate stones. Patients with complete distal renal tubular acidosis are treated with alkali in sufficient quantities so as to increase to normal their serum bicarbonate concentration. (Broadus, 1981) When alkali abuse resulting in a "milk-alkali" syndrome or an acetazolamide induced secondary renal tubular acidosis is suspected, then it would seem appropriate to withdraw these medications from a patient's treatment regimen. If other risk factors for stone disease (e.g hypouresis, hypercalciuria) are

also present, these, too, should be investigated and, it would seem, be treated appropriately.

Calcium Oxalate Stones

As suggested above, rational approaches to the understanding of garden-variety calcium stones might benefit from understanding the underlying type of stone disease that the patient has. An initial determination would be whether the calcium oxalate stone is a secondary manifestation of a primary disease such as primary hyperparathyroidism, distal renal tubular acidosis, enteric hyperoxaluria, or sarcoidosis. Presumably, treatment of the underlying disease would head off the formation of stones. Once a primary disease has been ruled out, the risk factor approach can prove most useful. In this series, a risk factor for calcium oxalate stone disease could be identified in over three-fourths of patients with the garden-variety type of stone. With low urine volumes, hypercalciuria, and hyperuricosuria all being potentially modifiable, theoretical understanding of risk factors might be usefully applied to reducing risk of recurrent stone formation. Patients producing a urine volume of below one liter per day might be instructed to increase their water intake regularly. Dietary modifications may also be made. Unnecessary pharmacologic doses of Vitamin C should be eliminated from the patient's intake. (Smith, 1978) Because it is metabolized to oxalic acid, the removal of excess Vitamin C can lead to a significant decrease in oxalate excretion through the urine.

For the risk factor of hyperuricosuria associated with calcium oxalate stones, several important points may be made. The fractional excretion of uric acid is no greater in the "garden-variety" stone-formers with hyperuricosuria than in the remainder of the stone population. Nevertheless, their level of serum uric acid and their average level of purine intake is higher than that of the remainder of the stone

population. In addition, the correlation between dietary purine/kg Wt and urinary uric acid/kg Wt is highly significant for the entire stone population (p=.006). Taken together, these facts suggest (but, of course, do not prove) that the hyperuricosuria seen in the calcium oxalate stone population is not caused by a defect in the excretion of uric acid, but rather reflects purine gluttony. Although treatment modalities were beyond the scope of this study, if this hypothesis were true, it would provide a rational explanation for the so-called "Western diet" acting to predispose patients to renal calculi. Presumably, if this hypothesis were true, hyperuricosuric calcium oxalate stone formers might be able to reduce the degree of or eliminate one of their risk factors for stones by modifying their dietary intake of purines. In practice, most such patients are treated with allopurinol.

The pathophysiological mechanisms responsible for "idiopathic" hypercalciuria are controversial. In the present series, the majority of hypercalciuric patients displayed evidence of the specific syndrome of so-called absorptive hypercalciuria. As an extension of the present series, these patients were evaluated in detail, and an increase in circulating $1,25\text{-}(OH)_2D$, the hormonal form of vitamin D responsible for the regulation of intestinal calcium transport, was observed in eighty per cent of patients. (Broadus, 1984) The "phosphate-leak" hypothesis is a recent proposal put forth to explain this constellation of findings. In essence, this hypothesis holds that the primary abnormality in affected patients is a proximal tubular "leak" of phosphate, leading to secondary stimulation of $1,25\text{-}(OH)_2D$ synthesis (known to be sensitive to hypophosphatemia) and the remaining features of the syndrome. The findings of this series do not support this hypothesis, in that a tendency toward a reduction in TmP/GFR and hypophosphatemia was found in both hypercalciuric and non-hypercalciuric patients, indicating that hypophosphatemia could not regularly

and/or statistically be related to circulating 1,25-$(OH)_2D$ or, in fact, even hypercalciuria, in patients with calcium oxalate stone disease. (Broadus, 1984) Although this point is controversial (Tschöpe, 1980), the findings in this series in this regard are in agreement with the only other large series in which this question was examined systematically. (Edwards, 1965) Based on these and other observations in patients with this syndrome, an alternate pathogenetic theory has been proposed. (Broadus, 1984)

There is no consensus regarding optimal medical therapy for the treatment of this form of hypercalciuria. (Broadus, 1981) Diet may be approached through an increased fluid and a decreased (about 400 mg/day) calcium intake. It is possible that a restriction in calcium intake may be physiologically compensated for by an increased oxalate absorption and excretion--so negating potential benefits of reducing calcium intake alone. (Broadus, 1981) Sodium cellulose phosphate, which is nonabsorbable and can complex with calcium, has been reported to be effective in reducing calcium excretion in patients with absorptive hypercalciuria. (Pak, 1974) If all other approaches fail, therapy may also be instituted empirically. Thiazides have been reported highly effective in moderating undifferentiated hyperoxaluria and hypercalciuria, and oral phosphorus has been reported to increase the excretion of pyrophosphate, an inhibitor of stone formation and growth. (Yendt, 1978, Thomas, 1978, Pak, 1979)

The identification of a subpopulation of "dietary hypercalciurics" is an extremely important component if one wishes to appreciate the nature of hypercalciuria. In this series "dietary hypercalciurics" were defined among the garden-variety calcium oxalate stone population as being those hypercalciuric patients whose 24 hour calcium excretion on a free diet was at least 50 mg than their calcium excretion on a

fixed 1000-mg calcium diet or who met the condition that they be hypercalciuric on both the fixed and free diets, yet have a normal response to a calcium tolerance test. This population excretes an especially high level of calcium on a diet that on the basis of its calcium content alone should not predispose to hypercalciuria. If the statistical association between dietary sodium intake and urinary calcium excretion on a free intake diet that was established in this group bears out in physiological terms, then it would seem that their hypercalciuria might partially result from dietary factors. In particular, a high sodium diet would tend to predispose patients in this subpopulation to hypercalciuria and, presumably, renal calculi. If the converse of this hypothesis is true, then a restricted sodium diet in this group of patients might reduce urine calcium excretion and, presumably, decrease a patient's chances of developing renal calculi.

Possibly, by eliminating as many risk factors as possible, calcium oxalate stone disease, indeed, most renal stones, might largely be prevented.

## APPENDIX ONE--NUMERICAL DATA

All Patients:

| Category | Number | Mean | Std Dev |
|---|---|---|---|
| Age at First Episode (yrs) | 226 | 34 | 12 |
| Frequency of Episodes (#/yr) | 217 | 2 | 4 |
| Serum Calcium (mg/dl) | 229 | 9.6 | 0.6 |
| Serum Uric Acid (mg/dl) | 227 | 6.2 | 1.7 |
| Serum Phosphate (mg/dl) | 229 | 3.2 | 0.5 |
| Serum Carbon Dioxide (mEq/L) | 228 | 26.1 | 3.1 |
| Serum Chloride (mEq/L) | 228 | 104 | 3 |
| Dietary Calcium (mg/day) | 217 | 569 | 330 |
| Dietary Calcium (mg/kg Wt/day) | 217 | 7.7 | 4.7 |
| Dietary Oxalate (mg/day) | 217 | 47 | 51 |
| Dietary Oxalate (mg/kg Wt/day) | 217 | 0.67 | 0.87 |
| Dietary Liquid (ml/day) | 195 | 2014 | 842 |
| Dietary Liquid (ml/kg Wt/day) | 195 | 28 | 13 |
| Dietary Purine (mg/day) | 217 | 128 | 94 |
| Dietary Purine (mg/kg Wt/day) | 217 | 1.7 | 1.3 |
| Dietary Protein (g/day) | 217 | 89 | 35 |
| Dietary Protein (g/kg Wt/day) | 217 | 1.20 | 0.48 |
| Dietary Sodium (mg/day) | 217 | 2175 | 1215 |
| Dietary Sodium (mg/kg Wt/day) | 217 | 29.4 | 18.1 |
| Dietary Phosphorus (mg/day) | 216 | 1225 | 516 |
| Dietary Phosphorus (mg/kg Wt/day) | 216 | 16.5 | 6.8 |

| | | | |
|---|---|---|---|
| Urine Volume (ml/day) | 229 | 1607 | 808 |
| "Free" Urine Calcium (mg/day) | 227 | 229 | 117 |
| "Free" Urine Calcium (mg/kg Wt/day) | 227 | 3.05 | 1.51 |
| "Fixed" Urine Calcium (mg/day) | 222 | 248 | 114 |
| "Fixed" Urine Calcium (mg/kg Wt/day) | 222 | 3.30 | 1.50 |
| Urine Sodium (mEq/day) | 113 | 150 | 73 |
| Urine Sodium (mEq/kg Wt/day) | 113 | 1.95 | 0.85 |
| Fractional Excretion of Uric Acid | 38 | 0.068 | 0.033 |
| Urine Uric Acid (mg/day) | 228 | 669 | 251 |
| Urine Uric Acid (mg/kg Wt/day) | 228 | 8.83 | 3.08 |
| Urine Oxalate (mg/day) | 31 | 55 | 38 |
| Urine Oxalate (mg/kg Wt/day) | 31 | 0.75 | 0.54 |
| Urine Phosphorus (mg/day) | 222 | 959 | 401 |
| Urine Phosphorus (mg/kg Wt/day) | 222 | 12.7 | 4.7 |
| Low Urine pH | 223 | 5.3 | 0.6 |
| Mean Urine pH | 109 | 5.8 | 0.7 |
| TmP/GFR | 203 | 3.1 | 0.7 |
| Urine Culture (Organisms/ml) | 203 | 11300 | 74000 |

Magnesium Ammonium Phosphate Stone Patients:

| Category | Number | Mean | Std Dev |
|---|---|---|---|
| Urine Volume (ml/day) | 9 | 1771 | 834 |

| | | | |
|---|---|---|---|
| "Free" Urine Calcium (mg/day) | 9 | 196 | 115 |
| "Free" Urine Calcium (mg/kg Wt/day) | 9 | 2.3 | 1.7 |
| "Fixed" Urine Calcium (mg/day) | 9 | 190 | 173 |
| "Fixed" Urine Calcium (mg/kg Wt/day) | 9 | 2.5 | 1.3 |
| Urine Uric Acid (mg/day) | 9 | 611 | 272 |
| Urine Phosphorus (mg/day) | 9 | 1029 | 573 |
| TmP/GFR | 9 | 2.4 | 0.6 |
| Urine Culture (Organisms/ml) | 8 | 45600 | 47800 |

Uric Acid Stone Patients:

| Category | Number | Mean | Std Dev |
|---|---|---|---|
| Serum Calcium (mg/dl) | 6 | 9.7 | 0.4 |
| Serum Uric Acid (mg/dl) | 6 | 7.0 | 2.0 |
| Urine Volume (ml/day) | 6 | 1000 | 378 |
| "Free" Urine Calcium (mg/day) | 6 | 157 | 67 |
| "Free" Urine Calcium (mg/kg Wt/day) | 6 | 2.0 | 0.8 |
| "Fixed" Urine Calcium (mg/day) | 6 | 239 | 124 |
| "Fixed" Urine Calcium (mg/kg Wt/day) | 6 | 3.0 | 1.7 |
| Fractional Excretion of Uric Acid | 2 | 0.085 | |
| Urine Uric Acid (mg/day) | 6 | 656 | 321 |
| TmP/GFR | 6 | 3.0 | 0.6 |

Cystine Stone Patients:

| Category | Number | Mean | Std Dev |
|---|---|---|---|
| Serum Calcium (mg/dl) | 3 | 9.6 | 0.4 |
| Urine Volume (ml/day) | 3 | 1160 | 299 |
| "Free" Urine Calcium (mg/day) | 3 | 156 | 125 |
| "Free" Urine Calcium (mg/kg Wt/day) | 3 | 1.9 | 1.5 |
| Urine Cystine (mg/day) | 3 | 811 | 564 |
| Urine Uric Acid (mg/day) | 3 | 878 | 649 |
| TmP/GFR | 2 | 3.9 | |

Calcium Phosphate Stone Patients:

| Category | Number | Mean | Std Dev |
|---|---|---|---|
| Serum Calcium (mg/dl) | 17 | 9.5 | 0.4 |
| Serum Carbon Dioxide (mEq/L) | 17 | 25.2 | 3.0 |
| Urine Volume (ml/day) | 17 | 1361 | 518 |
| "Free" Urine Calcium (mg/day) | 17 | 242 | 141 |
| "Free" Urine Calcium (mg/kg Wt/day) | 17 | 3.3 | 1.8 |
| "Fixed" Urine Calcium (mg/day) | 17 | 281 | 104 |
| "Fixed" Urine Calcium (mg/kg Wt/day) | 17 | 3.8 | 1.4 |

| | | | |
|---|---|---|---|
| Mean Urine pH | 11 | 6.0 | 0.3 |
| Urine Uric Acid (mg/day) | 17 | 602 | 205 |
| Urine Phosphorus (mg/day) | 17 | 878 | 280 |
| TmP/GFR | 14 | 2.8 | 0.8 |

Calcium Phosphate Stone Patients without RTA, or a History of Antacid Abuse or Acetazolamide Ingestion:

| Category | Number | Mean | Std Dev |
|---|---|---|---|
| Urine Volume (ml/day) | 12 | 1337 | 548 |
| Mean Urine pH | 7 | 6.1 | 0.2 |
| "Free" Urine Calcium (mg/day) | 12 | 248 | 145 |
| "Free" Urine Calcium (mg/kg Wt/day) | 12 | 3.4 | 1.9 |
| "Fixed" Urine Calcium (mg/day) | 12 | 282 | 115 |
| "Fixed" Urine Calcium (mg/day) | 12 | 3.9 | 1.6 |
| Urine Uric Acid (mg/day) | 12 | 618 | 115 |
| Urine Phosphorus (mg/day) | 12 | 863 | 240 |
| TmP/GFR | 10 | 2.9 | 0.9 |

Calcium Oxalate Stone Patients with Sarcoidosis:

| Category | Number | Mean | Std Dev |
|---|---|---|---|
| Serum Calcium (mg/dl) | 2 | 10.2 | |
| Serum Uric Acid (mg/dl) | 2 | 8.4 | |
| Serum Phosphate (mg/dl) | 2 | 3.2 | |
| Urine Volume (ml/day) | 2 | 1750 | |
| "Free" Urine Calcium (mg/day) | 2 | 188 | |
| "Free" Urine Calcium (mg/kg Wt/day) | 2 | 2.78 | |
| "Fixed" Urine Calcium (mg/day) | 2 | 365 | |
| "Fixed" Urine Calcium (mg/kg Wt/day) | 2 | 5.17 | |
| Urine Uric Acid (mg/day) | 2 | 632 | |
| Urine Phosphorus (mg/day) | 2 | 1240 | |

Calcium Oxalate Stone Patients with Enteric Hyperoxaluria:

| Category | Number | Mean | Std Dev |
|---|---|---|---|
| Serum Calcium (mg/dl) | 8 | 9.3 | 0.5 |
| Urine Volume (ml/day) | 8 | 1231 | 316 |
| "Free" Urine Calcium (mg/day) | 8 | 147 | 71 |
| "Free" Urine Calcium (mg/kg Wt/day) | 8 | 2.1 | 1.1 |
| "Fixed" Urine Calcium (mg/day) | 8 | 119 | 26 |
| "Fixed" Urine Calcium (mg/kg Wt/day) | 8 | 1.7 | 0.5 |
| Urine Uric Acid (mg/day) | 8 | 514 | 126 |
| Urine Uric Acid (mg/kg Wt/day) | 8 | 7.14 | 2.24 |

| | | | |
|---|---|---|---|
| Urine Phosphorus (mg/day) | 8 | 703 | 280 |
| Urine Phosphorus (mg/kg Wt/day) | 8 | 9.98 | 5.01 |
| Urine Oxalate (mg/day) | 5 | 74 | 19 |
| Urine Oxalate (mg/kg Wt/day) | 5 | 1.0 | 0.3 |
| TmP/GFR | 8 | 3.2 | 0.87 |

Calcium Oxalate Stone Patients with Primary Hyperparathyroidism:

| Category | Number | Mean | Std Dev |
|---|---|---|---|
| Serum Calcium (mg/dl) | 9 | 11.2 | 1.1 |
| Urine Volume (ml/day) | 9 | 1577 | 571 |
| "Free" Urine Calcium (mg/day) | 10 | 326 | 154 |
| "Free" Urine Calcium (mg/kg Wt/day) | 10 | 3.9 | 1.3 |
| "Fixed" Urine Calcium (mg/day) | 8 | 396 | 158 |
| "Fixed" Urine Calcium (mg/kg Wt/day) | 8 | 5.1 | 1.9 |
| Urine Uric Acid (mg/day) | 10 | 714 | 268 |
| Urine Phosphorus (mg/day) | 9 | 1102 | 563 |
| TmP/GFR | 7 | 2.7 | 0.7 |

Garden-Variety Calcium Oxalate Stones:

| Category | Number | Mean | Std Dev |
|---|---|---|---|
| Serum Calcium (mg/dl) | 179 | 9.6 | 0.5 |
| Urine Volume (ml/day) | 179 | 1644 | 844 |
| "Free" Urine Calcium (mg/day) | 178 | 233 | 111 |
| "Free" Urine Calcium (mg/kg Wt/day) | 178 | 3.1 | 1.4 |
| "Fixed" Urine Calcium (mg/day) | 177 | 251 | 105 |
| "Fixed" Urine Calcium (mg/kg Wt/day) | 177 | 3.3 | 1.4 |
| Urine Uric Acid (mg/day) | 178 | 679 | 242 |
| Urine Uric Acid (mg/kg Wt/day) | 178 | 8.9 | 3.0 |
| Urine Phosphorus (mg/day) | 173 | 983 | 401 |
| Urine Phosphorus (mg/kg Wt/day) | 173 | 12.8 | 4.6 |
| Urine Oxalate (mg/day) | 31 | 40 | 43 |
| Urine Oxalate (mg/kg Wt/day) | 31 | 0.53 | 0.60 |
| TmP/GFR | 160 | 3.1 | 0.7 |

Calcium Oxalate Stone Patients with Low Urine Volume:

| Category | Number | Mean | Std Dev |
|---|---|---|---|
| Age at First Stone Event (Years) | 36 | 32 | 10 |
| Urine Volume (ml/day) | 36 | 1022 | 338 |
| "Free" Urine Calcium (mg/day) | 36 | 166 | 71 |
| "Free" Urine Calcium (mg/kg Wt/day) | 36 | 2.32 | 0.97 |
| "Fixed" Urine Calcium (mg/day) | 35 | 189 | 62 |

| | | | |
|---|---|---|---|
| "Fixed" Urine Calcium (mg/kg Wt/day) | 35 | 2.67 | 0.99 |
| Urine Uric Acid (mg/day) | 36 | 578 | 215 |
| Urine Uric Acid (mg/kg Wt/day) | 36 | 8.16 | 3.35 |
| Urine Phosphorus (mg/day) | 34 | 866 | 428 |
| Urine Phosphorus (mg/kg Wt/day) | 34 | 12.1 | 5.6 |

Calcium Oxalate Stone Patients with Hyperuricosuria:

| Category | Number | Mean | Std Dev |
|---|---|---|---|
| Serum Calcium (mg/dl) | 57 | 9.6 | 0.4 |
| Serum Uric Acid (mg/dl) | 57 | 6.8 | 1.6 |
| Dietary Purine (mg/kg Wt/day) | 56 | 1.9 | 1.4 |
| Dietary Purine (mg/day) | 56 | 156 | 104 |
| Urine Volume (ml/day) | 57 | 2030 | 1112 |
| Urine Uric Acid (mg/day) | 57 | 956 | 152 |
| Fractional Excretion of Uric Acid | 16 | 0.076 | 0.034 |
| Urine Phosphorus | 57 | 1246 | 458 |
| "Free" Urine Calcium (mg/day) | 57 | 267 | 123 |
| "Fixed" Urine Calcium (mg/day) | 57 | 261 | 113 |

Calcium Oxalate Stone Patients with Absorptive Hypercalciuria:

| Category | Number | Mean | Std Dev |
|---|---|---|---|
| Serum Phosphate (mg/dl) | 56 | 3.1 | 0.5 |
| Urine Volume (ml/day) | 56 | 1780 | 794 |
| "Free" Urine Calcium (mg/day) | 56 | 308 | 97 |
| "Fixed" Urine Calcium (mg/day) | 56 | 331 | 81 |
| Urine Uric Acid (mg/day) | 56 | 675 | 219 |
| Urine Phosphorus (mg/day) | 56 | 1018 | 397 |
| TmP/GFR | 56 | 3.1 | 0.7 |

Calcium Oxalate Stone Patients with Dietary Hypercalciuria:

| Category | Number | Mean | Std Dev |
|---|---|---|---|
| Urine Volume (ml/day) | 23 | 1962 | 937 |
| "Free" Urine Calcium (mg/day) | 23 | 394 | 89 |
| "Fixed" Urine Calcium (mg/day) | 23 | 285 | 80 |
| Urine Uric Acid (mg/day) | 23 | 800 | 250 |
| Urine Phosphorus (mg/day) | 23 | 1191 | 376 |
| TmP/GFR | 20 | 3.0 | 0.8 |

## APPENDIX TWO--METHODS AND FORMS

Initial contact with patients occurred by telephone. On this important occasion the patients were instructed as to what to expect in the evaluation of his stone disease. They were told that they would be sent a 24-hour urine specimen container, which they were to bring with them to their first clinic appointment. They were also sent the "Diet History Instruction Form" (see following page) which told them how to record their dietary intake. Finally, they were instructed to arrive at his first renal stone clinic visit in a state of fasting, so that the initial screening tests of blood and urine were on standardized samples.

## DIET HISTORY INSTRUCTION FORM

1. You are to write down everything you eat and drink for a period of three days that you consider to be representative of what you usually eat, with attention to the following:
   a. The three days do not need to be consecutive.
   b. One of the days you keep a record of what you eat and drink should be the same day you do a 24 hour collection of urine (please specify this day clearly in your booklet).
2. Use this booklet to keep a record of your food intake.
3. Include the complete amounts you eat and what time you eat.
4. Estimate the portion size of all foods and list measures for all items. For example, an average size chicken leg is about 3 oz. of meat, while 1 slice of cold cuts is about 1 oz. of meat. All beverages, canned fruits, vegetables and cereals should be measured with a measuring cup, not a coffee cup.
5. Be sure to include butter, margarine or fat if used with vegetables or bread; gravies or sauces; condiments such as mustard, catsup, mayonnaise or salad dressings; and milk, cream or sugar used in coffee or tea and on cereal.

   Here is an example:

| | |
|---|---|
| 7:00 A.M. | ½ grapefruit with 2 teaspoons of sugar<br>1 egg<br>2 strips bacon<br>1 toast with 1 teaspoon butter |
| 10:00 A.M. | 1 cup coffee with 2 tablespoons of evaporated milk and 2 teaspoons of sugar<br>1 sweet roll with 1 pat margarine |
| 12:00 Noon | 1 large fried hamburger<br>½ cup mashed potatoes with 2 tablespoons gravy<br>½ cup peas with 1 teaspoon of margarine<br>1 glass (8 oz.) milk<br>½ cup fruit cocktail<br>2 chocolate filled cookies |
| 3:15 P.M. | Mounds candy bar |

6. If you encounter any problems or have questions concerning your recall, please call during Tuesday morning clinic hours and ask to speak to the dietitian regarding your diet. The phone number is (203)-436-8060.

On arrival at the renal stone clinic, the patient is given a copy of the form reproduced below:

"FIRST RENAL STONE CLINIC VISIT"

Your first Renal Stone Clinic visit is designed to obtain:

a) A clinical history and physical examination by the physician.

b) A detailed dietary history obtained by the nutritionist.

c) Initial screening tests of blood and urine.

d) The initiation of a search for a history of kidney stones in your family.

In addition, your initial visit is designed to allow for further diagnostic laboratory testing under optimum conditions. This testing includes:

a) Collection of two 24-hour urine specimens while you are eating a defined 1000 mg calcium diet.

b) Many patients will have an x-ray examination (either plain x-rays of the kidneys or an intravenous pyelogram). If you are to have any type of kidney x-ray, you will be given a packet of material concerning preparation for this x-ray. Please note that this preparation would interfere with the 24-hour urine collections, so that in no case should a 24-hour specimen of urine be collected during preparation for x-rays. For patients living in the metropolitan New Haven area, the x-rays will be scheduled at a time several or more days distant from the urine collections. For patients coming from a longer distance, the 24-hour specimens may be collected and refrigerated for a day during which time the preparation for x-rays is taking place (in this case begin the x-ray preparation the day before the scheduled x-ray rather than following the two day instructions included in the packet).

# RENAL STONE CLINIC H & P FORM

I. Name:
Address:
Telephone number:
Age:
Sex:

II. Referring physician:
Address:
Telephone number:

III. Clinical stone events. Specify date, side, and type (passed, removed, historical event, or radiologic new stone) of each event.

Total number__Stones per patient year__Bilateral?__

IV. Previous evaluation:
a. Stone analysis (% composition, laboratory name):
b. Chemistries:
c. C & S and pH:
d. IVP:
e. Date and findings on last x-ray:

V. Prior treatment. Specify when instituted, estimate of compliance, and estimate of benefit.
a. Forced fluids:
b. Diet:
c. Medication:
d. Present or recent medications (when discontinued):

VI. Past history:
a. Childhood illnesses:
b. Adult illnesses:
c. Hospitalizations:
d. Operations:
e. Allergies:

VII. Clinical and social history.
a. Abnormal serum or urinary calcium:
b. Abnormal serum or urinary uric acid:
c. Hyperparathyroidism:
d. Gout:
e. Ulcer disease (dyspepsia):
f. Antacid intake:
g. Analgesic intake:
h. Vitamin intake:
i. Chronic diarrhea:

j. Hypertension:
k. Kidney or bladder infection:
l. Osteoporosis, bone pain, fractures:
m. Sun exposure:
n. Periods of dehydration:
o. Work:
p. Smoking:
q. Ethanol:
Comments and/or Review of Systems:

VIII. Dietary summary:

IX. Family history summary:

X. Physical examination:
1. HEENT:
2. Chest:
3. Abdomen:
4. Genitalia:
5. Extremities:
6. Neurologic:

XI. Summary:

At the conclusion of the first stone clinic appointment, the patient is given a detailed instruction form explaining the procedure for collecting a 24-hour urine on a defined 1000 mg calcium intake:

"INSTRUCTIONS FOR TWO 24-HOUR URINE COLLECTIONS ON A 1000 MG CALCIUM INTAKE"

1. These collections are ideally performed on the weekend following your first Renal Stone Clinic visit, and the detailed instructions below assume that you intend to collect these specimens on the weekend. Any equivalent period of time is satisfactory, and you may modify the instructions below for your own convenience.

2. Friday morning (1 day before beginning the urine collections) begin eating the diet on which you were instructed by the nutritionist. Also begin to take the calcium gluconate tablets, two tablets with each meal (6 tablets per day). Please note that these tablets are large and should be chewed to a fine powder before swallowing. Continue the diet and the calcium tablets on Saturday and Sunday, the two days of urine collections.

3. Estimate what time you will get up on the following Monday morning, and write this time in the three blanks below.

SATURDAY

4. ___a.m.: Void into the toilet as usual. (You may go back to bed after voiding). The next time you void, collect the urine into a clean container and pour it carefully

into one of the collection jugs. The collection jugs contain an acid preservative, so that you should not void directly into them. Continue to collect all urine passed; refrigerate the collection bottle during and after completion of the collection.

SUNDAY

5. _____a.m.: Void and add this urine to the same bottle you were using on Saturday; this completes the first 24-hour specimen. The next time you void, pour the urine into a new collection jug. Continue to collect all urine passed, and refrigerate the specimen.

MONDAY

6. ___a.m.: Void and add this urine to the bottle you were using on Sunday; this completes the second 24-hour specimen.

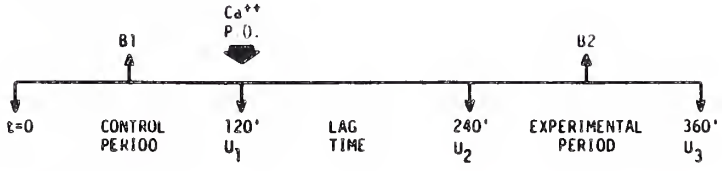
7. Label each bottle carefully with the date of the collection (e.g. 3/17-3/18/77).

8. The collection jugs should be returned to the clinic on DANA III. Please do not eat or drink anything before bringing the specimens to the clinic; you are scheduled to have a blood specimen drawn on the same morning.

# FLOW DIAGRAM AND DATA BASE DERIVED FROM THE ORAL CALCIUM TOLERANCE TEST (BROADUS, 1978, 1981)

ORAL CALCIUM TOLERANCE TEST

I. FLOW DIAGRAM




II. DATA BASE

A. STATIC MEASUREMENTS (CONTROL PERIOD)

1. BASAL SERUM CALCIUM & PHOSPHOROUS
2. FASTING CALCIUM EXCRETION
3. FASTING TMP/GFR
4. BASAL NEPHROGENOUS OR TOTAL cAMP EXCRETION
5. BASAL VITAMIN O METABOLITES

B. DYNAMIC MEASUREMENTS (EXPERIMENTAL VS CONTROL PERIOD),

1. CALCEMIC RESPONSE AS INDEX OF "CALCIUM TOLERANCE"
2. CALCIURIC RESPONSE (Δ mg CALCIUM/100 ML GF) AS INDEX OF GI ABSORPTION
3. SUPPRESSIBILITY OF NEPHROGENOUS OR TOTAL cAMP EXCRETION

Patients were prepared for the calcium tolerance test test by following a restricted (about 400 mg/day) calcium diet for ten days prior to testing and by fasting except for distilled water beginning at 8 p.m. the night before the test began. Patients were hydrated with 8 ounces of distilled water semi-hourly, beginning at 7 a.m. and continuing through the completion of the test. At 7 a.m., the urine was voided and discarded. At 8 a.m., a serum calcium specimen was obtained. At 9 a.m. a urine specimen was obtained. An oral dose of approximately one gram of elemental calcium (administered as 35 ml of calcium glubionate syrup plus 8 ounces of lactase-treated milk) was administered at 9 a.m., immediately following the first urine collection. At 11 a.m. a urine sample was collected and discarded. At 12 noon, another serum sample was obtained. The test finally concluded with a last urine collection at 1 p.m.. Except for voiding, the patients remained inactive betwee 8 a.m. and 1 p.m. on the test day. The three collection periods represented a fasting control period, a two-hour lag period in which peak calcium absorption could occur, and an experimental period that demonstrated the maximal systemic effects of the absorbed calcium. The calciuric response was calculated by subtracting the rate of calcium excretion during the control period from that during the experimental period. Calcium excretion rates were calculated by using the formula: CaE=Urine Calcium X Serum Creatinine/Urine Creatinine. The upper-normal limit for the calciuric response is 0.2 mg calcium per 100 ml GF. Absorptive hypercalciuria was diagnosed in patients who met the following criteria: 1) Calcium excretion rate greater than 300 mg/day and/or greater than 4 mg/kg/day on the 1000-mg calcium diet, 2) Hyperabsorption of calcium (as measured by the calciuric response to the calcium tolerance test, and 3) normal or suppressed parathyroid function in the fasting state (Nephrogenous cAMP less than 2.7 nmol/dL GF). (Broadus, 1984) Total urinary cAMP was determined with the formula: Total

UcAMP=Urinary cAMP X Serum Creatinine/Urine Creatinine. Nephrogenous cAMP was determined by subtracting the plasma cAMP level (i.e. the filtered load of cAMP) from the total amount of cAMP excreted.

Data were analyzed by means of the unpaired t-test and univariate linear regression, all performed on the CLINFO system at the Clinical Research Center at the Yale-New Haven Medical Center.

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